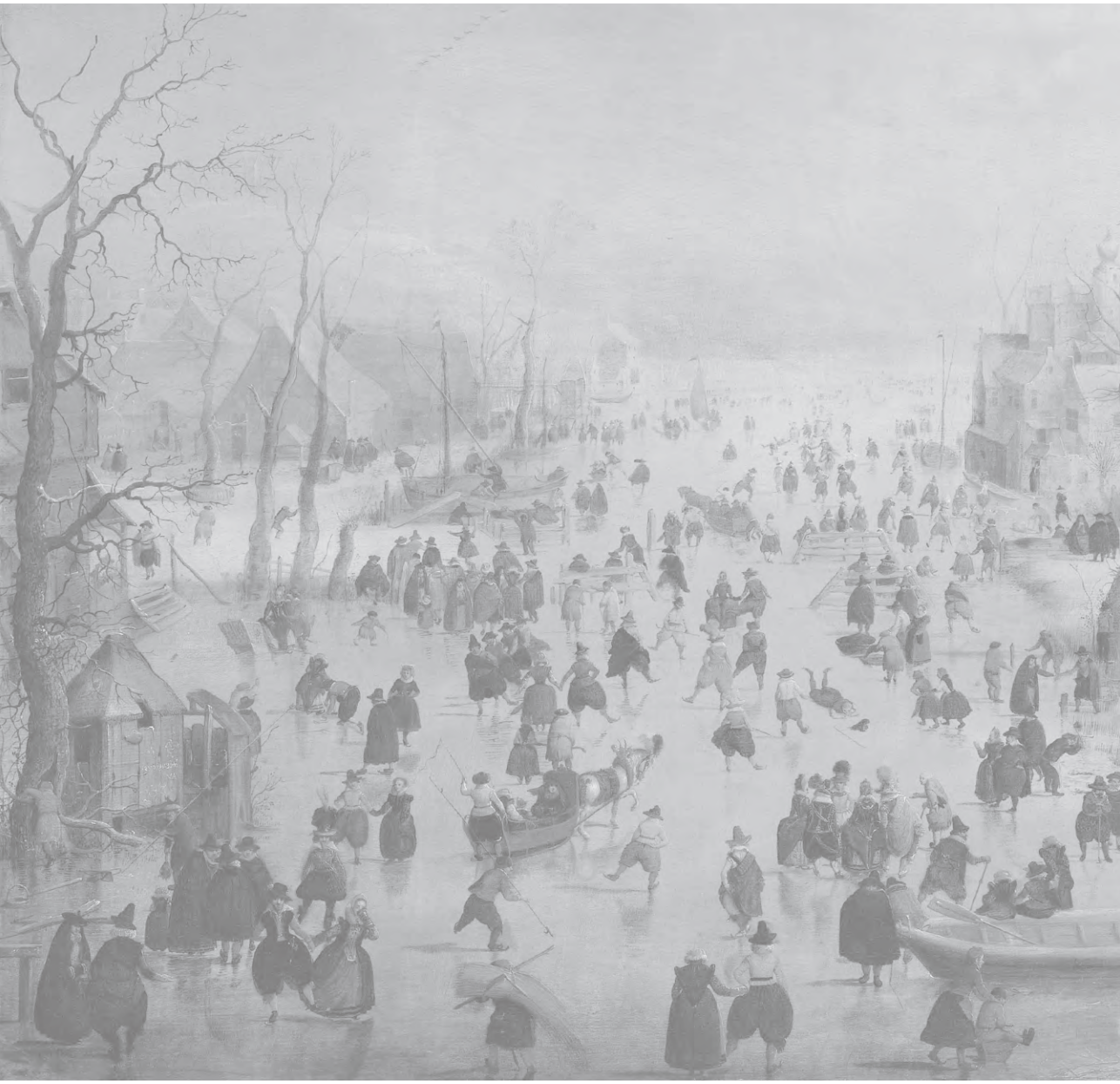
Personalized treatment targets in rheumatoid arthritis

Yvonne M.R. Vendrig – de Punder



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Colofon

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Table of contents

De wetenschap brengt kennis over de werking der dingen

Verhalen brengen begrip

Fragment uit *Iedereen is een verhaal – Parkinson*,
HoutenBeenTheater 2013

General introduction

1

Rheumatoid Arthritis (RA) is an autoimmune disease that is characterized by symmetrical synovitis, mainly of the small joints of the hands and feet; pain; fatigue and morning stiffness. Sometimes extra-articular manifestations are present, such as rheumatoid nodules or vasculitis. An important consequence of the inflammatory process in RA is joint damage of cortical bone and cartilage. If untreated, joint damage may have already occured in the first three years of the disease. Both the inflammation as well as the joint damage can lead to functional disability.[1]

The prevalence of RA is estimated at 0.5-1% in Western Europe. In the Netherlands this resulted in 11000 newly diagnosed patients in 2011.[2] The exact cause of RA is still unknown, but it is regarded that genetic, immunologic and environmental factors play a role in its etiology. The strongest factors appear to be periodontal disease, smoking, a 'shared epitope' in the HLA system and occurrence of citrullinated peptides. In patients with a genetic predisposition, cigarette smoking and periodontal disease can cause citrullination which activates cells in the synovial lining of small joints, causing arthritis and joint damage.[1,3]

As RA currently cannot be cured or prevented, the goal of medical treatment in RA is suppression of inflammation and pain relief, as well as prevention of the long-term consequences such as joint damage and disability. Several types of medication are used in the treatment of RA, usually in combination. The medication that is commonly used are synthetic Disease Modifying anti-Rheumatic Drugs (sDMARDs), biological DMARDs (bDMARDs), corticosteroids and Non-Steroid Anti Inflammatory Drugs (NSAIDs). Particularly methotrexate and the bDMARDs have shown to be very effective treatments for RA, with the drawback of the bDMARDs being quite expensive. When medication is stopped, this is usually because of toxicity or insufficient effect, but may also be because of sufficiently low disease activity or remission.

With the current available treatment options, the ultimate treatment goal is remission, meaning silencing of the disease process.[4,5] However, complete remission and sustained remission are still reached only in a minority of RA patients, even if treated with biological DMARDs.[6,7]

According to the current Dutch and international treatment guidelines for RA, the treatment of first choice at the start of the disease is Methotrexate monotherapy.[4,8] In RA patients with poor prognostic factors, such as joint erosions at diagnosis, presence of anti-CCP and high levels of acute phase reactant, combination therapy of sDMARDs might be started at diagnosis.[4,8] When the response to treatment is insufficient after 3-6 months, the treatment may be switched to another sDMARD, or an sDMARD or bDMARD may be added.

When remission is reached early in the disease, there is a higher chance that remission will be sustained and that joint damage and other disease consequences can be prevented.[6]

Therefore the concept of treat-to-target has been developed. Treat-to-target means 1) setting a treatment target for the level of disease activity for every patient; 2) regular assessment of the disease activity; and 3) treatment according to a protocol that prescribes regular and quick adjustment of medication when the treatment goal is not reached. It has been proven in several studies that with the concept of treat-to-target the treatment goal of remission or low disease activity is reached more often and earlier in the disease.[9,10]

RA disease activity usually is measured by an index, containing several variables that measure different aspects of inflammation. Usually these indices include the number of swollen joints, the number of tender joints, the level of an acute phase reactant and a patient global rating of disease activity. Examples of these indices are Disease Activity Score (DAS) and Disease Activity Score for 28 joints (DAS28) or the Simplified Disease Activity Index (SDAI). In daily practice and in guidelines the Disease Activity Score with 28 joints is most often used. The DAS and DAS28 express the level of disease activity in a score between 0 and 10, in which a higher score represents more disease activity. Remission is defined as DAS28 < 2.6, or DAS < 1.6 when the full joint score and Ritchie score is used.[11,12]

The treat-to-target strategy is also feasible and effective in daily practice, notably using the disease activity score with 28 joints (DAS28).[11,13] In studies of treat-to-target, the disease activity score (DAS) is most often used to monitor disease activity.[9] However, in practice the Disease Activity Score of 28 joints (DAS28) is more often used to measure disease activity. Using the DAS28 in daily practice, the target can be low disease activity (DAS28 < 3.2) or remission (DAS28 < 2.6) for all RA patients. However, the question is whether the treatment target should be the same for all RA patients. We should consider moving away from 'one-size-fits-all' to a more personalized approach in setting treatment targets in RA. A key to that is, given the same level of inflammation, not all RA patients have the same risk of joint damage progression.[14,15]

Three main prognostic factors for joint damage progression have consistently been identified in RA at the moment of diagnosis: anti-CCP, Erythrocyte Sedimentation Rate (ESR) and presence of erosions.[16-21] These risk factors are applied in the current treatment guidelines for RA. Based on these three risk factors, patients are divided into two groups: patients at risk for joint damage progression and patients not at risk for joint damage progression. It is not clearly defined when patients are considered at risk, but usually when one of the three risk factors is present the patient is thought to be at risk for joint damage progression. In these patients sDMARD combination therapy or an early switch to bDMARDS is advised.[4,7,8,19] This way, the management of treatment in RA is becoming more personalized, based on the risk factors for unfavourable prognosis that a patient has at the start of the disease .

Based on the knowledge about the three main prognostic factors for development

of joint damage progression and the relation between disease activity and joint damage progression, the current treat-to-target strategies can be ameliorated in two ways.[4,8] First, this dichotomy of the patients qualified being 'at risk' or being 'not at risk' for joint damage progression can be further specified by combining the three main baseline risk factors for quantification of the risk for unfavourable prognosis. Knowing these risks is important in clinical decision making when weighing the benefits and harm of therapies. A patient who is anti-CCP positive, has no erosions at diagnosis and has low ESR will presumably develop less joint damage than an anti-CCP positive patient with erosions and high ESR at diagnosis. Several studies have been done for the quantification of this risk in a so called matrix model.[17,22-24] The reader can judge the risk by applying patient characteristics to the matrix and then read the risk for that patient. These models are user-friendly for daily clinical practice, but not widely used yet. Possibly this is because the developed matrix models appeared not to be generalizable in external validation.[25,26] Another way of combining the three risk factors was therefore explored.

Moreover, the quantified risk for joint damage progression at diagnosis could be combined with the most important dynamic risk factor in RA: disease activity over time. As alluded to above, at the same level of disease activity, a patient without the three main risk factors, i.e. anti-CCP negative, no erosions and an a low level of ESR at the moment of diagnosis, will probably have a lower risk for joint damage progression than an anti-CCP positive patient, with erosions and a high level of ESR at the moment of diagnosis. The disease activity treatment target for the second patient conceivably should be lower than for the first patient. Personalization of the treatment target might guide more individualized treatment choices in daily clinical practice, when the ultimate goal, sustained drug-free remission, is not reached.

The aim of this thesis was to study how disease activity targets for the treat-to-target strategy in RA can be personalized. Therefore we quantified the individual risk for joint damage progression in RA during the first three years of the disease, based on the presence of the three main prognostic factors for joint damage progression: anti-CCP, acute phase reactant and erosions at the moment of diagnosis. We also analyzed the relationship between predefined disease activity levels and joint damage progression, being dependant of the three main prognostic factors for joint damage progression. Accordingly, the first steps towards personalized treatment targets for RA were taken.

In the clinically used disease activity indices, the treatment target remission does not require complete absence of all clinical symptoms, resulting in residual disease activity. The disease activity indices differ in the level of residual disease activity that is accepted. It is

still subject of discussion how much residual disease activity can be accepted in a patient without increasing the risk for long-term consequences, such as disability and joint damage. In **chapter 2** the achievability of different treatment targets in RA was studied. The strict 2010 ACR/EULAR remission criteria were compared to DAS28 < 2.6 remission and Minimal Disease Activity regarding prevalence, the presence of residual disease activity and the functional disability after six months of treatment with anti-TNF.

One of the most important serologic prognostic factors that can be used for personalizing RA treatment is anti-CCP. In **chapter 3** the difference in prognosis between anti-CCP negative and anti-CCP positive patients regarding joint damage progression was illustrated. Anti-CCP is thought to modify the relation between disease activity and joint damage progression. This means that at the same level of disease activity, anti-CCP positive patients develop more joint damage progression when compared to anti-CCP negative patients. It also means that to prevent joint damage progression, the level of disease activity over time should be lower in an anti-CCP positive patient than in an anti-CCP negative patient. It was shown how this might be translated to differentiation of treatment targets between those two groups.

Several prediction models for joint damage progression in RA have been developed. However, currently none of these models appears to be widely clinically used for personalization of the treatment of RA. This also regards the user-friendly matrix models. **Chapter 4** considers a study investigating whether further simplification of a prediction model for joint damage progression will result in loss of performance. For this aim, a simplified baseline prediction model was developed for prediction of joint damage progression and compared to an extended model based on the same prognostic factors anti-CCP, erosions and ESR at baseline, regarding discriminative and predictive ability.

In **chapter 5** four risk profiles were extracted from the simple prediction model developed in chapter 4, by simply counting the number of baseline risk factors for joint damage progression present in the individual patient: anti-CCP, ESR and erosions. Next to these 'static' baseline risk factors, disease activity is an important dynamic factor for prediction of the risk for joint damage progression. Therefore, the baseline risk profiles were combined with disease activity over time so that the probability for joint damage progression could be estimated at different levels of disease activity for each of the four risk profiles. It was shown how personalized treatment targets could be extracted from this prediction model.

This thesis is a step towards personalization of treatment targets in RA. In **chapter 6** the clinical implication of the results of the studies described from chapter 2 to 5 are discussed and placed in a broader perspective of personalized medicine. Steps for future research aiming for validation, generalization and refinement are explained.

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Röntgenlaborant: Naam.

Vivian: Mijn naam? Vivian Bearing.

Röntgenlaborant: Huh?

Vivian: Bearing. B-E-A-R-I-N-G. Vivian. V-I-V-I-A-N.

Röntgenlaborant: Dokter.

Vivian: Ja, ik heb een PhD.

Röntgenlaborant: Uw dokter.

Vivian: Oh. Dokter Harvey Kelekian. Ik ben doctor in de letteren,...

(ze wordt gepositioneerd voor de röntgenfoto)

Röntgenlaborant: Haal diep adem en houd dit vast.

(pauze) Okee.

Vivian: ... gespecialiseerd in de zeventiende eeuwse poëzie.

Röntgenlaborant: Draai opzij, armen achter uw hoofd.

(Pauze) Okee.

Vivian: Ik heb een enorme bijdrage geleverd aan het discipline van de Engelse literatuur. Ik ben, kort gezegd, een autoriteit op mijn vakgebied.

(ze wordt naar laborant 2 gebracht)

Röntgenlaborant 2: Naam.

Vivian: Lucy, Gravin van Bedford.

Röntgenlaborant 2: (Checkt de lijst) Dat staat niet op de lijst.

Vivian: Mijn naam is Vivian Bearing. B-E-A-R-I-N-G. Dokter Kelekian is mijn dokter.

Fragment uit *Als de dood,* Albert Verlinden Entertainment 2010

The prevalence of clinical remission in RA patients treated with anti-TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry

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P.M. Houtman
H. Visser
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2

Rheumatology (Oxford) 2012; 51: 1610-1617

Abstract

Objective

To evaluate the prevalence of clinical remission and minimal disease activity according to the ACR/EULAR remission, DAS28 < 2.6 and minimal disease activity criteria (MDA), and to compare the extent of residual disease activity and disability in RA patients after six months of treatment with anti-TNF.

Methods

In the DREAM biological registry the prevalence of DAS28 < 2.6, MDA, and ACR/EULAR remission criteria was assessed. Residual disease activity during MDA or remission was assessed as the percentage of patients with swollen and tender joints, elevated acute phase reactants and General Health on a Visual Analogue Scale (VAS). Disability was evaluated with the HAQ-score.

Results

Prevalence of DAS28 < 2.6 was 27%, prevalence of MDA was 34%, ACR/EULAR remission was reached by 6% of patients. Residual disease activity was present most in the most lenient criteria and occurred most frequently on the level of Swollen Joint Count and VAS-score: at least one swollen joint in DAS28 < 2.6, MDA and ACR/EULAR remission was present in respectively 51%, 54% and 34% of patients. VAS > 1 occurred in resp. 67%, 69% and 0%. Modification of the cut point of the patient reported outcome increased the prevalence of ACR/EULAR remission, but also the level of disability.

Conclusion

MDA and DAS28 < 2.6 are reachable treatment targets in RA with anti-TNF, although residual disease activity might still be present. In turn, ACR/EULAR remission criteria leave little residual disease activity, but might be too stringent for use in daily clinical practice due to the strict cut point in the patient reported outcome.

Introduction

Remission has become the ultimate target in the treatment of Rheumatoid Arthritis (RA). This is driven by the improved treatment options that became available during the last ten years, including the introduction of treatment with anti-TNF, and more intensive treatment control with traditional DMARDs such as methotrexate. However, remission is only reached in a minority of RA patients, and sustained remission is even more difficult to reach.[1]

Currently, there are several criteria for remission. Obviously, the number of patients in clinical remission that is found in clinical studies depends on the criteria used.[2-4] Criteria that are relatively lenient and allow some residual disease activity, such as the DAS28 < 2.6, may be reachable goals in clinical practice. Criteria that are relatively strict, such as the 1981 preliminary ACR remission criteria, may not be reached frequently.[5] However, treatment targets for RA do shift and the following question may be raised: What currently is the appropriate treatment target in RA?

The DAS28 < 2.6 remission criterion is frequently used in clinical studies. This criterion appears to be relatively lenient. Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are more strict by design, while the preliminary American College of Rheumatology (ACR) remission criteria are even more strict. Because of the observation that 'real' clinical remission did not occur frequently in daily clinical practice, the concept of minimal disease activity (MDA) was introduced in 2005. MDA was defined as a state of disease activity that could be a useful target of treatment by both physician and patient.[6] In 2011 new remission criteria for RA were presented that were jointly developed by ACR and EULAR.[7] These remission criteria were developed for clinical trials and according to the authors should be easy-to-use, achievable in practice and stringent in order to differentiate remission from low disease activity. In clinical trials, remission criteria are used to compare active medication with placebo or usual care on group level, while the goal of remission criteria in daily practice concerns the individual patient. Therefore, the ACR/EULAR remission criteria may be too strict also in daily clinical practice, especially due to the low cut point (≤ 1 cm) in the patient reported outcome.[8,9]

The objectives of this study were to determine reachable targets for treatment with anti-TNF in Rheumatoid Arthritis by studying the prevalence of remission and minimal disease activity according to three different criteria: DAS28 < 2.6, MDA and ACR/EULAR remission criteria; to show the presence of residual disease activity in the different criteria; and to evaluate the relation between residual disease activity and disability, in RA patients after 6 months of treatment with anti-TNF.

Patients and methods

Design

The DREAM (Dutch Rheumatoid Arthritis Monitoring)-biological registry is a prospective ongoing cohort study of RA patients treated with biologics that started in 2003. The registry contains data collected in 13 collaborating hospitals in the Netherlands. Data of RA patients that started using anti-TNF before 2003 at the department of Rheumatology at the Radboud University Nijmegen Medical Centre were collected in the predecessor of the DREAM-registry, which had the same inclusion criteria. For the current study data from the DREAM-registry and its predecessor were used of RA patients that started for the first time with anti-TNF. Prevalence of remission was studied at six months follow up, since the maximal effect of anti-TNF is observed between 3 to 6 months after start of therapy, while the average level of disease activity stays stable after 6 months (Figure 1).[10]

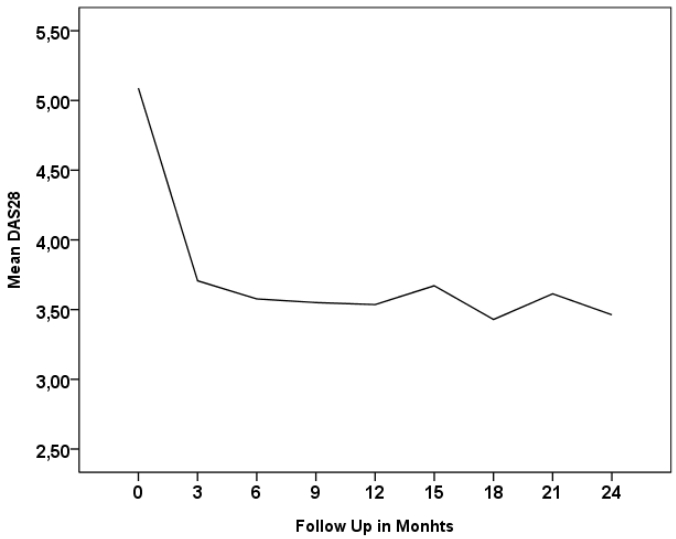

Figure 1. Mean DAS28 during the first 2 years of treatment with anti-TNF in Rheumatoid Arthritis

Patients

Inclusion criteria for the DREAM-biological registry were: a diagnosis of Rheumatoid Arthritis according to the 1987 ACR criteria, starting treatment with a biological treatment, and the presence of written informed consent. According to Dutch reimbursement rules, treatment with biological therapy is reimbursed in case of active disease (DAS28 > 3.2) after treatment failure of at least 2 DMARD's, including methotrexate. Patients were consecutively included in the cohort. Switch of biologic or stopping biologic treatment was not a reason for exclusion

from the cohort. For the current analysis, patients were included if they were treated with anti-TNF with a minimal duration of six months and if follow up data at 6 months were available.

Remission and minimal disease activity criteria

Criteria used in the analyses were the DAS28 < 2.6 criterion, MDA and the new ACR/EULAR remission criterion. DAS28 was calculated using the original formula with SJC28, TJC28, ESR and VAS General Health (VAS GH).[11,12] MDA was defined as: the presence of SJC28 = 0, TJC28 = 0 and ESR ≤ 10 mm/h; or presence of DAS28 < 2.85.[13] ACR/EULAR remission criteria are defined as: SJC28 ≤ 1, TJC28 ≤ 1, CRP ≤ 1 mg/dl, and Patient Global Assessment of Disease Activity (PtGA) ≤ 1 on a visual analogue scale of 10 cm.[7] In the DREAM cohort PtGA was not a standard measurement. We used VAS GH instead of PtGA in the calculations, because of the large agreement between patient global assessment of disease activity and general health measured on visual analogue scales. In a subset of patients with both assessments of VAS GH and PtGA at 6 months follow up, (N= 147) the ICC between PtGA and VAS GH was = 0.79 (p<0.0001). The mean difference between PtGA and VAS GH was approaching zero (0.11 cm, p=0.41), and the limits of agreement were +/- 32 mm. This suggests absence of a systematic error in presence of considerable random error, not leading to bias (figure 2).

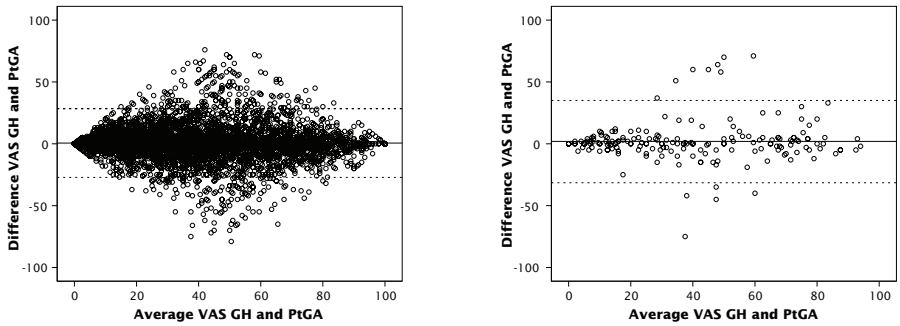

Figure 2. Limits of agreement between VAS General Health and Patient Global Assessment of disease activity shown by Bland-Altman plot. **A**. Agreement at all follow-up moments in the DREAM-cohort. **B**. Agreement at follow up 6 months.

In a previous study it has been shown that high values for the VAS assessment may occur even when SJC28, TJC28 and ESR are at a low or normal level.[8] Therefore, the performance of the ACR/EULAR criteria was also analyzed when modifying the patient reported outcome by

varying the cut point. CDAI, SDAI and (modified) ACR remission criteria could not be calculated because Physician Global Assessment of disease activity, morning stiffness, and fatigue were not standardly assessed in all periods of the DREAM-biological registry.

Residual disease activity

Residual disease activity was defined as any detectable disease activity, assessed by the number of swollen and tender joints, the acute phase reactants, with ESR > 20 mm/h in men and > 30 mm/h in women and CRP > 1 mg/dl, and by VAS GH > 1 (on a scale from 0 to 10 cm).

Disability

Disability was measure by the validated Dutch version of the Health Assessment Questionnaire on a scale from 0 to 3, in which a higher score signifies more disability.[14,15]

Analysis

The prevalence of remission and MDA and presence of residual disease activity as well as the level of disability were analyzed at 6 months after start with a first anti-TNF. Missing values for ESR (9%) were imputed based on age, sex, joint counts and CRP, using single imputation with a regression method including a random component.[16] Similarly, missing values for CRP (18%) were imputed based on age, sex, joint counts and ESR. Statistic testing of the prevalence and HAQ-scores between different criteria was not possible due to the study design with the same patients in the different groups.

Results

Patients

Until June 2010 there were 2220 patients included in the DREAM-registry and its predecessor that started their first anti-TNF treatment. Eleven percent of patients had stopped the anti-TNF treatment before 6 months (236/2220). Of 453 patients there were no joint counts available at 6 months follow up, leading to 1531 evaluable patients. The mean age of patients at start of their first anti-TNF agent was 54,4 years (SD 12,7) with a median disease duration of 71,0 months (IQR 25,0-156,0). Of all 1531 patients 68,5% (1049/1531) were female and 71,7% (1066/1487) were positive for IgM Rheumatoid Factor. At baseline the mean DAS28 was 5,00 (SD 1,32) and after 6 months of treatment the mean DAS28 was decreased with 1,51 ($p < 0.001$) to 3,49 (SD 1,34). Patients included in the analysis did not differ significantly or relevantly from patients not included in the analysis (results not shown).

At baseline 37% (562/1531) of patients started adalimumab, 42% (640/1531) etanercept and 21% (329/1531) infliximab. Fifty percent (772/1531) of patients used one concomitant DMARD and 40% (614/1531) of patients used two or more DMARDs concomitantly. Seventy-four percent (1139/1531) of patients used methotrexate and 36% (555/1531) of the patients used corticosteroids at baseline.

Remission and minimal disease activity criteria

The prevalence of clinical remission and MDA are presented in Table 1. Prevalence of DAS28 < 2.6 was 26,9%, while the prevalence of MDA (DAS28 < 2,85) was 33,9%. The prevalence of clinical remission according to the ACR/EULAR criteria was 6,1%. Agreement between DAS28 < 2,6 and MDA was 93 % (kappa 0.72), between DAS28 < 2.6 and ACR/EULAR remission agreement was 78 % (kappa 0.18) and between MDA and ACR/EULAR remission agreement was 72 % (kappa 0.14). Modification of ACR/EULAR remission criteria by increasing the cut point of VAS, increased the prevalence to 10.3% when VAS ≤ 2 and to 17.8% when VAS ≤ 4 (table 2).

N=1531	**DAS28 < 2.6**	**MDA**	**ACR/EULAR remission**
Prevalence	26,9% (412)	33,9% (519)	6,1% (93)
SJC = 0	49,0% (202)	46,2% (240)	65,6% (61)
= 1	19,9% (82)	19,5% (101)	34,4% (32)
≥ 2	31,1% (128)	34,3% (178)	0% (0)
SJC > 0	51,0% (210)	53,8% (279)	34,4%
TJC = 0	74,8% (308)	71,1% (369)	78,5% (73)
= 1	15,8% (65)	17,1% (89)	21,5% (20)
≥ 2	9,5% (39)	11,8% (61)	0% (0)
TJC > 0	25,2% (104)	28,9% (150)	21,5%
ESR elevated	1,0% (4)	2,9% (15)	5,4% (5)
CRP elevated	8,7% (36)	9,8% (51)	0% (0)
VAS GH > 1	67,2% (277)	69,4% (360)	0% (0)
HAQ-score	0.63 (0.25-1.09)	0.63 (0.25-1.13)	0.38 (0.13-0.63)

Table 1. Prevalence of MDA and clinical remission and occurrence of residual disease activity according to three different criteria. DAS28 = Disease Activity Score 28 joints, with cut point 2.6; MDA = Minimal Disease Activity was defined as DAS28 < 2,85 or SJC28 = 0, TJC28 = 0 and ESR ≤ 10 mm/h; ACR/EULAR remission was defined as SJC28 ≤ 1, TJC28 ≤ 1, CRP ≤ 1 mg/dl and VAS GH ≤ 1; SJC28 = swollen joint count 28 joints, TJC28 = tender joint count 28 joints, ESR elevated = erythrocyte sedimentation rate > 20 mm/h (male) or > 30 mm/h (female), CRP elevated = c-reactive protein > 1 mg/dl, VAS GH = patient assessment of General Health on a visual analogue scale from 0 to 10. HAQ-score = health assessment questionnaire score of patients in remission (median – IQR).

N=1531	VAS ≤ 1	VAS ≤ 2	VAS ≤ 3	VAS ≤ 4	No VAS
Prevalence	6,1% (93)	10,3% (157)	14,4% (221)	17,8% (272)	22,5% (345)
SJC = 0	65,6% (61)	63,7% (100)	65,6% (145)	65,1% (177)	66,1% (228)
= 1	34,4% (32)	36,3% (57)	34,4% (76)	34,9% (95)	33,9 (117)
TJC = 0	78,5% (73)	76,4% (120)	73,8% (163)	71,7% (195)	71,3% (246)
= 1	21,5% (20)	23,6% (37)	26,2% (58)	28,3% (77)	28,7% (99)
ESR elevated	5,4% (5)	7,0% (11)	8,6% (19)	11% (30)	11% (38)
HAQ	0.37 (0.13-0.63)	0.38 (0.13-0.63)	0.50 (0.13-0.88)	0.50 (0.25-1.00)	0.63 (0.25-1.13)

Table 2. Prevalence of remission and residual disease activity in the ACR/EULAR remission criteria, with modification of the cut point of Patient Global Assessment of General Health. SJC28 = swollen joint count 28 joints, TJC28 = tender joint count 28 joints, ESR elevated = erythrocyte sedimentation rate > 20 mm/h (male) or > 30 mm/h (female). HAQ = health assessment questionnaire score of patients in remission (median – IQR).

Residual disease activity

Residual disease activity occurred most on the level of SJC28 and VAS GH and less frequently in TJC28 and acute phase reactant (Table 1). At least one swollen joint was present in about half of the patients with DAS28 < 2.6 and MDA, but only in one third of the patients fulfilling the ACR/EULAR remission criteria; prevalence of residual tender joint(s) was more similar between the criteria varying from 22% in ACR/EULAR remission to 29% in MDA. VAS GH > 1 was present in two third of patients fulfilling DAS28 < 2.6 or the criteria of MDA. In the ACR/EULAR remission criteria residual disease activity in the patient reported outcome does not occur because VAS GH ≤ 1 cm was part of the definition.

Complete absence of tender and swollen joints and CRP ≤ 1 was reached by 183 of 1531 patients (12%). However, 130 (71%) of these patients were not in remission according to ACR/EULAR remission criteria due to a VAS score > 1. Analysis of the distribution of VAS GH in all 345 patients fulfilling the 3 more objective variables of the ACR/EULAR remission criteria, SJC ≤ 1, TJC ≤ 1 and CRP ≤ 1 mg/dl, showed that 79% had a VAS score ≤ 4. Therefore we modified the VAS GH cut point stepwise from 1 to 4. Increasing the cut point of VAS GH did not change the percentage of patients with one residual swollen joint. The percentage of patients with one tender joint increased gradually with the increasing VAS cut point (table 2). The same trend was seen for ESR. By definition CRP was in all these patients ≤ 1 mg/dl.

Disability

The median HAQ-score in ACR/EULAR remission is 0.38 and is lower than the HAQ of 0.63 in patients in DAS28 < 2.6 and MDA (fig 3). When modifying the cut point of VAS GH from

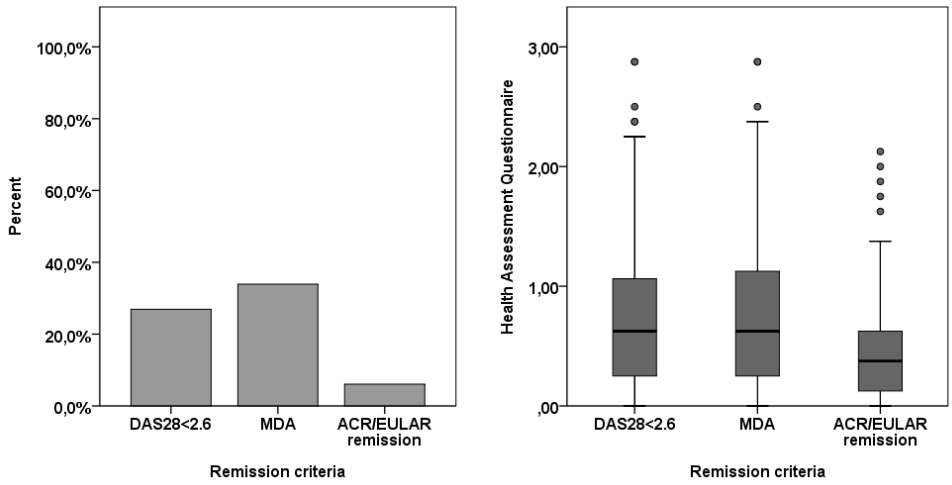

Figure 3. Prevalence of MDA and remission and median HAQ-score. A. Prevalence of MDA, DAS28 < 2.6 and ACR/EULAR remission. MDA was defined as DAS28 < 2.85 or SJC28 = 0, TJC28 = 0 and ESR ≤ 10 mm/h; ACR/EULAR remission defined as SJC28 ≤ 1, TJC28 ≤ 1, CRP ≤ 1 mg/dl and VAS GH ≤ 1. B. Median HAQ-score in patients with MDA, DAS28 < 2.6 or ACR/EULAR remission. HAQ = health assessment questionnaire; DAS28 = Disease activity score 28 joints.

1 to 2, the HAQ-score did not change. When the VAS cut point was increased to 3 or 4, the median HAQ increased from 0.38 to 0.50.

Discussion

The prevalence of remission and MDA after 6 months of treatment with anti-TNF in RA patients differed largely between criteria, according to the results of this study. MDA and DAS28 <2.6 were quite lenient with 26-33% and ACR/EULAR remission criteria were quite strict with 6% of patients being in remission at six months.

Obviously, residual disease activity occurred more frequently in the more lenient criteria. For DAS28 < 2.6 and MDA criteria most residual disease activity was present in the VAS GH > 1cm, up to 69% of patients in MDA. In the ACR/EULAR remission criteria no residual disease activity on the patient reported outcome was seen, because VAS GH < 1 cm was part of the criteria. The majority of patients with no swollen or tender joints and a CRP ≤ 1 mg/dl, who may be considered to be in clinical remission for an important extent, were not classified as being in remission according to the ACR/EULAR remission criteria because of their VAS score higher than 1 cm. Another striking result is that patients that score 1 on every item of ACR/EULAR remission criteria have a DAS28 of 2.8, which is higher than the

cut point of DAS28 remission. Because of these results and in addition VAS GH being the variable with most residual disease activity in DAS28 < 2.6 and MDA, it appears that the low cut point (≤ 1 cm) in the patient reported outcome of the ACR/EULAR remission criteria is too strict to be applied in daily clinical practice. When the criteria were modified, by varying the cut point of VAS GH stepwise to 4, the prevalence of remission raised to almost 18%.

Our last objective, to evaluate the relation between residual disease activity and disability, showed that more residual disease activity also led to increased disability scores. This was shown when comparing ACR/EULAR remission to the more lenient criteria, but also in the increasing HAQ when modifying the cut point of VAS in the ACR/EULAR remission criteria.

RA patients may have a different prognosis for joint damage progression based on the presence of e.g. shared epitope, anti-CCP positivity or RF positivity. This implies that ACR/EULAR remission must not be the most appropriate treatment target for all RA patients. In presence of less favorable prognostic factors such as anti-CCP and 'residual' presence of swollen joints, pharmacological treatment may be intensified, if not leading to unacceptable toxicity.

The prevalence of remission and MDA differs between health care systems and countries.[2-4] The prevalence of 25% in DAS28 <2.6, as found in our study, falls well within the range of prevalences found in other daily practice studies of anti-TNF that varied from 16% to 32%.[17-20] The differences in prevalence may depend on follow up time, disease duration and baseline disease activity. MDA is less frequently reported than DAS28 <2.6 in clinical studies. Three trials with adalimumab and abatacept showed a prevalence of MDA of 15% - 31%.[21,22] In two cohorts of RA patients using non biologic DMARDs, a prevalence of MDA was found of 20%-23%.[23,24] Prevalence of ACR/EULAR remission in cross-sectional analysis in cohorts of daily practice was 7,5% to 8.8%.[25,26]

Residual disease activity, especially of swollen joints is a known feature in DAS28 < 2.6. This is explained by the fact that low scores in one variable can compensate for high scores in others and the relatively low weight for swollen joints in the DAS28 formula. In our cohort 51% of patients had one or more swollen joint, which is higher than the range 9-30% found in literature. 25% of patients had tender joints when DAS28 < 2.6. This is in agreement with 8-40% of patients with DAS28 < 2.6 in other studies.[27-29] Residual disease activity in MDA or ACR/EULAR remission criteria is not previously published.

In literature the HAQ-score accepted in remission is 0.5, standing for hardly any difficulties in daily activities. HAQ of 1.0 stands for mild disability with some difficulties in all activities.[30] The median HAQ-score of patients in ACR/EULAR remission is below the cut point of 0.5. After modification of the VAS cut point to 3 or 4, the median HAQ did not pass

0.5. The interquartile range of the HAQ became higher, but does not extend the cut point for mild disability.

Treatment targets for RA are shifting. True clinical remission, which can be defined as complete absence of clinical signs and symptoms, is still difficult to reach. Minimal disease activity (MDA) or DAS28 < 2.6 might be a more reachable treatment target in practice. MDA and DAS28 < 2.6 appear to perform quite similar regarding prevalence as well as the occurrence of residual disease activity. Given the amount of residual disease activity allowed for in DAS28 < 2.6, it proposedly rather describes a state of near-remission or minimal disease activity just like MDA does.

ACR/EULAR remission criteria were developed to define a strict, though achievable target that distinguishes remission from low disease activity. By its construction the ACR/EULAR remission criteria effectively decrease the presence of residual disease activity as measured by tender, swollen joints and acute phase reaction, but they seem hard to achieve.

It is debatable whether or not a PtGA ≤ 1 is mandatory for remission of disease activity. Obviously a low PtGA is aimed at when the goal is to restore health. According to the authors, a patient reported outcome (PRO) should be included in the definition, as was shown by a CART-analysis. However, the cut point for Patient global Assessment was chosen for practical reasons.[7] There are reasons to regard that the cut point of 1 cm is inappropriately low. First, the cut point of 1 assumes that PtGA in patients without RA patients would be ≤ 1. However, 45% of the normal population aged 50 or older scores VAS GH > 2/10.[31] Second, the PtGA might be misinterpreted, because it does not only measure RA disease activity. The PRO is included in the definition of ACR/EULAR remission because it should convey morning stiffness, fatigue and other not objectively assessable disease activity. High correlations between VAS disease activity, pain and general health show that it is difficult for patients to distinguish RA activity from other ailments like accompanying osteoarthritis or myalgia. Additionally, several mechanisms separated from arthritis do influence patients' evaluation of their health, such as recalibration of the visual analogue scale after treatment (response shift), patients being more sensitive to losses than to gains (loss aversion), and the tendency of people not to rate extremes (end of scale aversion) apparently are not considered in the choice for the cut point.[32] Because of this unrealistic low cut point this variable has a very heavy weight in the ACR/EULAR definition of remission and remission is hard to achieve.

Remission as the ultimate goal in RA is questionable, because the definition of remission is still a matter of discussion. More important is to have reachable treatment targets based on disease outcomes as functionality. When PtGA is modified in the criteria, prevalence

increases considerably, but disability score increases also. This shows that it is desirable to include a Patient reported outcome in the definition of remission. However, it is unknown to what extent variation in the VAS cut point compromises the validity of the criteria.

The presented results concern a cohort of patients with established RA and a median disease duration of 6 years. However, from a treatment viewpoint it is highly relevant to try to reach remission in early RA. Moreover, remission, notably also with the ACR/EULAR remission criteria, may be more easily reached in early RA.[33] The time point of 6 months that was chosen for our analyses may be perceived to be short. However, this time point was chosen because the largest decrease of disease activity in patients with established RA has occurred in the first 6 months after start with anti-TNF treatment, and because the average level of disease activity stays stable after 6 months. Illustratively, occurrence of remission was not different between 6 and 12 months of follow-up. We also regarded that 6 months is a meaningful time point to show the much-wished-for beneficial effect of anti-TNF in RA patients failing DMARD therapy.

Due to the large amount of missing data of the variables Physician Global Assessment and Patient Global Assessment (PtGA) for disease activity in the DREAM dataset, we used only the DAS28-based definitions of MDA and the ACR/EULAR remission criteria based on SJC28, TJC28, CRP and PtGA. This is a limitation of our study. Further, PtGA rating was substituted by VAS GH in our calculation of the of ACR/EULAR remission criteria. The concept rated by the VAS GH is not the same as the concept rated by the VAS disease activity, because general health can also be caused by other factors than disease activity. However, VAS GH and PtGA by the patient were closely correlated and there was no systematic difference between the two variables. Therefore, we regard that at least in our study the ACR/EULAR remission criteria would not have performed differently with PtGA instead of general health.

In the definition of MDA ESR is used as acute phase reactant, while in ACR/EULAR remission CRP is chosen. Therefore the criteria are difficult to compare on the acute phase reactant. The aim of our study was to compare three different criteria, not to compare performance of CRP to ESR. We chose to present residual activity of both variables because of difference in common use or preference of rheumatologists.

In conclusion, MDA and DAS28 < 2.6 are reachable treatment targets in daily clinical practice for anti-TNF treatment of RA. However, both are associated with the presence of residual disease activity. In contrast, ACR/EULAR remission criteria show limited residual disease activity, but are not easily reached in clinical practice mainly because of the strict cut point on PtGA ≤ 1 cm.

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Taal is maar woorden

De interpretatie daar gaat het om

En die is subjectief

Die is altijd rijp voor miscommunicatie.

Fragment uit *Dag en nacht*, Theatergroep Plezant 2009

Should we redefine treatment targets in rheumatoid arthritis? Low disease activity is sufficiently strict for patients who are anticitrullinated protein antibody-negative

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3

J Rheumatol 2013; 40: 1268-1274

Abstract

Objective

Clinical remission currently is the treatment target for all RA patients. However, at the same level of inflammation the prognosis regarding joint damage is supposed to be different for anti-CCP negative and anti-CCP positive patients. The objective of this study was to show the difference in prognosis at similar disease activity levels and to illustrate how this could be translated to differentiation of treatment targets.

Methods

Data were used from the Nijmegen early RA Cohort. The relation between the time averaged disease activity level (DAS) and joint damage progression over 3 years was analyzed, separately for anti-CCP negative and anti-CCP positive patients. Joint damage was assessed as change in Ratingen score, and dichotomized as occurrence of erosions in joints that were unaffected at baseline. Linear and logistic multivariable regression models were used.

Results

The regression coefficient of DAS on change in Ratingen score was 3.9 ($p < 0.001$) for anti-CCP negative and 4.7 ($p < 0.001$) for anti-CCP positive patients, showing less joint damage progression at the same disease activity level in anti-CCP negative patients. This difference became larger with increasing disease activity. The probability for erosions in at baseline unaffected joints was 0.35 in anti-CCP negative patients when time averaged DAS was < 2.4 versus 0.80 in anti-CCP positive patients.

Conclusion

At the same level of inflammation anti-CCP negative patients have less joint damage and lower probability for damage in newly affected joints than anti-CCP positive patients. Low disease activity might be a sufficiently strict treatment targets for anti-CCP negative patients to prevent joint damage progression.

Introduction

RA is a multifactorial disease with joint erosions as a hallmark. As joint damage is largely irreversible, an important goal of RA treatment is to prevent joint damage.[1] In general more RA inflammation results in more joint damage.[2,3] Prevention of joint damage can thus be achieved by striving for remission, which is the ultimate treatment goal in RA. Quick switch or addition of medication is advised if remission is not achieved after 3 to 6 months of treatment.[4] However, the probability for future joint damage is not the same for all RA patients and treatment guidelines advise to take into account factors that predict poor prognosis when considering early or late switch to biologics.[5]

One of the main baseline factors predicting worse prognosis regarding joint damage is anti-CCP positivity.[6-9] Anti-CCP positive and negative RA are generally considered as two different entities of the same disease, because anti-CCP positive patients are reported to have more progression of joint damage progression as well as higher levels of inflammation than anti-CCP negative patients.[10,11] However, the difference in prognosis cannot be completely explained by the higher inflammation level. The relation between joint damage and inflammation is also different for anti-CCP positive and anti-CCP negative patients. Consequently, a level of inflammation that will result in a clinically relevant quantity of joint damage in anti-CCP positive patients will result in no or little joint damage in anti-CCP negative patients. Absence or presence of anti-CCP antibodies in a patient should thus not only be taken into account when considering the intensity of the treatment that is given, but could also result in a refinement of the one-size-fits-all treatment target of remission. This is especially important since sustained remission is still difficult to reach and patients are often satisfied with a state of low or even moderate disease activity.[12-15] When the risk for progression of joint damage is limited and the patient is satisfied with his or her symptom state, there remain no strong arguments for remission as a treatment goal for RA patients.

The objective of this study is to analyze the difference in joint damage progression between anti-CCP negative and anti-CCP positive RA patients in the first three years of the disease at the same level of disease activity, and to show that different treatment targets could be used for anti-CCP negative as compared to anti-CCP positive RA patients to prevent joint damage progression.

Methods

Design

Data were used from the database of the Nijmegen early RA cohort, an inception cohort of Rheumatoid Arthritis since 1985.[16] Because of resource limitations, joint damage scores

were only available in a subset of patients, who were included from 1985 until August 2002. For the current analyses data of the first three years of follow-up of these patients were used. No formal approval of a Medical Ethical Committee had to be obtained, because for this kind of observational studies this is not required in the Netherlands. All patients provided written informed consent to be included in the cohort.

Patients

Patients were consecutively included in the Nijmegen early RA cohort if they had a diagnosis of Rheumatoid Arthritis according to the 1987 ACR criteria for RA, had a disease duration less than one year, had no prior use of DMARDs and were aged 18 years or older. Accuracy of the diagnosis of RA was tested in a random subsample of 30 (34%) anti-CCP negative patients and only in 2 of the 30 patients the diagnosis had been revised, and after the third year. Therefore, we assumed that misclassification was appropriately low. Because of the high specificity of anti-CCP for RA we considered no doubt about the classification of anti-CCP positive RA.

Cohort patients were included for the current study if scored X-rays of hands and feet were available at baseline and at two or three years follow-up, if patients had at least 3 visits with assessment of the original disease activity score (DAS) including at least one visit in the third year, and if their anti-CCP status was known. Patients treated with biological response modifiers during the first three years were excluded from the current study, because this medication changes the relation between disease activity and joint damage.[17,18]

Assessments

Baseline characteristics of all patients were collected, including anti-CCP and Rheumatoid Factor. Anti-CCP was assessed using Anti-CCP2 Enzyme Linked Immuno Assay (ELISA Immunoscan RA Mark 2; Euro-Diagnostica, Malmo, Sweden) with a cut off value of > 25 U/ml considered positive. In a subset of patients this was determined post-hoc from frozen blood samples using fluoroenzymeimmunoassay for anti-CCP (EliA-CCP, Thermo Scientific, Uppsala, Sweden) with a cut off value of > 10 U/ml considered positive. The correlation between the two tests was 0.91. Disease activity was assessed every three months by trained research nurses using the swollen joint count of 44 joints (SJC), tender joint count of 53 joints (TJC) with grading according to Ritchie, Erythrocyte Sedimentation Rate (ESR) and a patient reported rating of general health on a visual analogue scale from 0 to 100 mm. The Disease Activity Score (DAS) was calculated according to the original formula.[19] X-rays of hands and feet were taken at baseline, 1, 2 and 3 years follow up. The X-rays of hands and feet of a single patient were read in chronological order by one of four raters

according to the Ratingen score using reference pictures.[20] The Ratingen score (range 0-198) is a modification of the Larsen score and evaluates the amount of joint surface destruction, graded from 0 to 5 in 38 hand and feet joints. The inter-rater reliability (ICC) was 0.85, tested previously with the 4 raters in 10 patients over 9 years of follow up.

The primary outcome of this study was the change in Ratingen score between baseline and three years follow up, representing the quantity of the progression. However, not only the quantity of joint damage progression is important for the prognosis, but also if the number of damaged joints increases. This is considered important, because it reflects the extent of joint damage and because joints that are already damaged have higher chance to show progression in the future.[21] Therefore, occurrence of new erosions in at baseline unaffected joints was the secondary outcome in this study. Inflammation was assessed using the time averaged DAS over 3 years time, calculated using the area under the curve of DAS and observation time, divided by observation time.

Analyses

First it was analyzed whether there were baseline differences between anti-CCP negative and positive patients using the chi-square test, the independent t-test or the Mann-Whitney U test, as appropriate. The relation between inflammation and joint damage progression was analyzed separately for anti-CCP negative and anti-CCP positive patients using linear regression with the change in Ratingen scores as the dependent variable (primary outcome). Ratingen Score at baseline was used as a covariate, age and sex were considered as confounders. Rheumatoid factor was not considered as confounder because of its close association with anti-CCP. To analyze the occurrence of newly damaged joints (secondary outcome) logistic regression was used, with at least one newly affected joint considered as progression and the same covariate and confounders. Because next to anti-CCP presence of erosions at baseline itself is an important risk factor for joint damage progression, additional analyses were done in which the models were not corrected for Ratingen score at baseline, but stratified by presence of erosions at baseline (≥ 1 Ratingen point). A regression coefficient with P-value < 0.05 was considered as a significant relation.

Missing values for X-ray scores at 3 years follow up were imputed using the Last Observation Carried Forward principle with the restriction that the X-ray was made during the third year. Missing values for ESR (3%) and VAS GH (6%) were imputed using single imputation, including a random component, based on sex, age, CRP and TJC.[22] The Statistic Package for Social Sciences (SPSS) Chicago ILL, version 18.0 was used for all statistical analyses.

Results

Patients

Until August 2002 448 patients had been included in the Nijmegen early RA cohort. Ratingen scores at baseline and follow up were available for 308 patients. Of these patients 301 (97%) had 3 or more disease activity assessments with at least one visit in the third year. In 281 (91%) of these patients anti-CCP status was known. Thirteen patients had used biological response modifiers during the first 3 years and were excluded. Consequently 267 of 448 (60%) patients that were included in the cohort until August 2002, were included for the analyses. The median number of disease activity assessments of these patients was 10 [IQR 7 – 18]. Imputation of the X-ray at 3 years was needed in 45 (17%) of 267 patients.

Patient characteristics, disease activity and joint damage

Baseline characteristics of the patients included in the study are presented in table 1. Anti-CCP negative patients were significantly older and less frequently positive for Rheumatoid Factor as compared to anti-CCP positive patients. There were no differences between the patient groups in parameters of disease activity, except for ESR at baseline and follow-up that were lower in anti-CCP negative patients. Presence of joint damage at baseline and progression of joint damage over three years was significantly lower in the anti-CCP negative patients.

Most RA patients were treated with DMARD monotherapy or in combination (table 1). Combination therapy was more frequently prescribed for anti-CCP positive patients. Few patients were not treated with DMARDs but with glucocorticosteroids or NSAIDs instead, which occurred more frequently in anti-CCP negative patients. There were no apparent differences in glucocorticosteroids use between anti-CCP negative and –positive patients, except for dose of oral glucocorticosteroids. No biologics were used by any patient, as this was an exclusion criterion for the study.

Disease activity score and joint damage progression

The relations between time averaged DAS and the change in Ratingen score (primary outcome) are presented in table 2. Linear regression models showed that DAS was strongly associated to joint damage progression in both anti-CCP negative and positive patients. In anti-CCP negative patients there was an increase (regression coefficient) of 3.9 ($p<0.001$) Ratingen points per point increase in average DAS, which was 4.7 ($p < 0.001$) for anti-CCP positive patients (figure 1A). Calculating the mean progression for an example RA patient, a 55 year old woman with no baseline erosions, with a time averaged DAS < 1.6 over three

		Anti-CCP negative N = 87	Anti-CCP positive N = 180	p-value
Age at diagnosis (yrs)		60 (14)	54 (12)	0.001
female		67% (58)	60% (107)	0.255
IgM RF positive		44% (38)	93% (167)	< 0.001
Number of visits		10 [8-14]	11 [8-22]	0.297
Baseline SJC		14 [10-23]	14 [10-20]	0.317
Baseline ESR		22 [9-45]	38 [15-56]	0.005
Baseline DAS		3.9 (1.3)	4.0 (1.2)	0.580
Baseline TJC		14 [6-21]	12 [6-19]	0.882
Baseline VAS GH		48 (25)	45 (24)	0.386
Time Averaged SJC		9 [5-11]	9 [6-12]	0.137
Time Averaged ESR		14 [8-25]	19 [10-29]	0.042
Time Averaged DAS		2.6 (0.9)	2.9 (0.9)	0.041
Ratingen Score Baseline		0 [0-1]	1 [0-3]	0.001
Ratingen Score 3 years		1 [0-8]	9 [3-19]	< 0.001
Change Ratingen 0-3 years		0 [0-6]	7 [2-16]	< 0.001
Newly damaged joints 0-3 years		48% (42)	82% (148)	< 0.001
DMARD	Combination therapy	76% (66)	75% (135)	0.056
	Mono-therapy	14% (12)	21% (38)	
	None	12% (9)	4% (7)	
Methotrexate use		41% (36)	38% (69)	0.351
Corticosteroids	total	56% (49)	61% (110)	0.455
	Oral < 15mg	9% (8)	15% (27)	0.048
	Oral ≥ 15 mg	13% (11)	5% (9)	

Table 1. Patient characteristics of the study population at baseline and during three years follow up, stratified by anti-CCP status. The values are mean (SD), median [P25-P75] or percentage (number) and the used statistical tests were independent t-test, Mann-Whitney U test, and chi-square test, as appropriate. IgM RF = Rheumatoid Factor, SJC = swollen joint count 44 joints, ESR = erythrocyte sedimentation rate, DAS = disease activity score, TJC = tender joint count 53 joints, VAS GH = general health scored on a visual analogue scale. Time averaged SJC, ESR and DAS are measured during 3 years follow up.

Model		Beta	95% CI	p-value
Anti-CCP negative	DAS	3.32	1.11-5.53	0.004
	Constant	-3.575	-9.69-2.55	0.249
	DAS	3.87	2.01-5.74	< 0.001
	Baseline Score	1.36	0.98-1.75	< 0.001
	Age	-0.11	-0.24-0.01	0.068
	Sex	-2.58	-6.23-1.07	0.163
	Constant	3.81	-6.52-14.15	0.465
Anti-CCP positive	DAS	4.46	2.70-6.22	< 0.001
	Constant	-2.17	-7.46-3.31	0.421
	DAS	4.70	2.96-6.45	< 0.001
	Baseline Score	0.81	0.51-1.11	< 0.001
	Age	-0.11	-0.24-0.03	0.120
	Sex	-1.77	-4.98-1.44	0.278
	Constant	3.54	-5.62-12.69	0.447

Table 2. Linear regression models for the relation between time averaged DAS and change in Ratingen score, stratified by anti-CCP status. Baseline Ratingen Score was added as co-variate to both models, age and sex were considered as confounders.

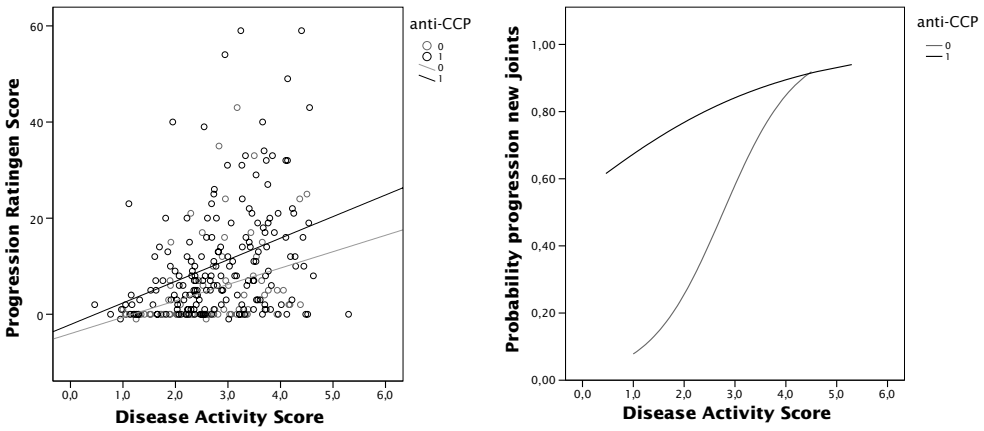

Figure 1. Relation between DAS and joint damage progression, stratified by anti-CCP status. A. Relation between time averaged DAS and the amount of joint damage progression (uncorrected model). B. Relation between time averaged DAS and the probability of occurrence of newly damaged joints (uncorrected model). DAS = Disease Activity Score.

years (remission), would result in no progression of Ratingen score over 3 years for both

an anti-CCP negative and anti-CCP positive patient. An average DAS between 1.6 and 2.4 (low disease activity) would result in no progression in an anti-CCP negative patient and 3 points in an anti-CCP positive patient. An average DAS between 2.4 and 3.7 (moderate disease activity) results in 6 points progression in anti-CCP negative versus 9 points in anti-CCP positive patients, while an average DAS > 3.7 (high disease activity) would result in progression of 7 Ratingen points in the anti-CCP negative patient as compared to 14 Ratingen points in the anti-CCP positive patient (figure 2).

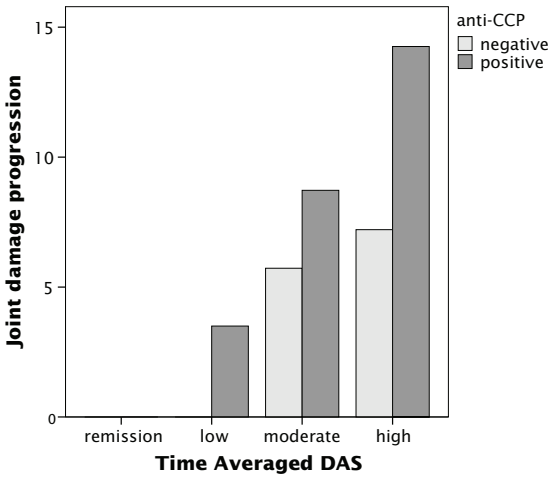

Figure 2. Mean joint damage progression (Ratingen score), calculated for an average patient (female, 55 years old, no baseline erosions), stratified by anti-CCP status. Remission = DAS < 1.6, low = DAS 1.6-2.4, moderate = DAS 2.4-3.7, high = DAS > 3.7.

In the former analyses Ratingen score at baseline was used as a co-variate. Next, the difference in association between DAS and change of Ratingen score between the anti-CCP negative and –positive group was analyzed for patients with and without baseline erosions separately. In the subgroup with joint damage at baseline there was a strong association between DAS and change of Ratingen score, however the difference between anti-CCP positive and negative patients disappeared and the regression coefficients were 5.7 and 5.6 respectively. Contrarily, in the group of patients without baseline erosions, the difference in association became larger with a regression coefficient of 2.4 in anti-CCP negative patients as compared to a regression coefficient of 3.7 in anti-CCP positive patients.

Disease activity score and probability for newly damaged joints

The relation between time averaged DAS and presence of erosions in at least one at baseline unaffected joint is presented in table 3. Disease activity was associated with an increase in affected joints after 3 years in both anti-CCP negative and anti-CCP positive patients. The group of anti-CCP negative patients had a smaller intercept and a larger regression coefficient and odds ratio (OR) than the group of anti-CCP positive patients. This corresponds with a low baseline risk and strong increase in the probability of newly damaged joints at a higher level of inflammation in anti-CCP negative patients, while the baseline risk in anti-CCP positive patients is already high and is not much further increased by an increasing level of inflammation. This resulted in a net lower risk in anti-CCP negative patients at low or moderate levels of inflammation than in anti-CCP positive patients. In figure 1B it is illustrated that with an average DAS of 2.4 (low), the probability to develop erosive progression in a previously unaffected joint was 0.35 in an anti-CCP negative patient and 0.80 in an anti-CCP positive patient. When stratified by presence of erosions at baseline, it appeared that the difference between anti-CCP negative and anti-CCP positive patients was larger in the subgroup of patients without baseline erosions, than in the patients with baseline erosions.

Model		Beta	OR	95% CI OR	p-value
Anti-CCP negative	DAS	1.24	3.47	1.88-6.40	< 0.001
	Constant	-3.31	0.037		< 0.001
	DAS	1.47	4.36	2.03-9.36	< 0.001
	Baseline Erosions	0.69	2.00	1.19-3.36	0.009
	Age	-0.01	0.99	0.95-1.03	0.643
	Sex	0.46	1.59	0.46-5.51	0.467
	Constant	-4.78	0.01		0.008
Anti-CCP positive	DAS	0.51	1.66	1.07-2.56	0.022
	Constant	0.15	1.17		0.801
	DAS	0.61	1.85	1.13-3.02	0.014
	Baseline Erosions	0.18	1.20	0.99-1.46	0.062
	Age	0.01	1.01	0.76-1.05	0.571
	Sex	-1.20	0.30	0.12-0.77	0.012
	Constant	0.99	2.69		0.429

Table 3. Logistic regression models for the relation between time averaged DAS and occurrence of newly damaged joints, stratified by anti-CCP status. Baseline Ratingen Score was added as co-variate to the models, age and sex were considered as confounders.

Anti-CCP positive patients without baseline erosions had a probability of 0.70 at low disease

activity (DAS 2.4), as compared to a probability of 0.25 in anti-CCP negative patients. The probabilities in patients with baseline erosions were 0.70 and 0.90 in anti-CCP negative and anti-CCP positive patients respectively.

Discussion

According to the results of this study, anti-CCP negative RA patients had less progression of joint damage as compared to anti-CCP positive patients at the same time averaged level of disease activity between baseline and 3 years follow up. The difference between the two groups increased with an increase of disease activity. It was also shown that at low levels of inflammation anti-CCP positive patients already have a higher probability than anti-CCP negative patients to develop erosions in new joints, but there is no difference between both groups if disease activity is high. In absence of joint damage at diagnosis, these differences between anti-CCP positive and – negative patients in the development of joint damage at similar levels of disease activity became even more pronounced.

Based on our results it can be hypothesized that treatment targets in disease activity for the prevention of joint damage progression may be different for anti-CCP negative and anti-CCP positive RA patients. It appears that most anti-CCP negative patients develop no or little joint damage progression in a state of remission or low disease activity. Within moderate disease activity, joint damage progresses, but the probability for an increase in the number of damaged joints becomes much higher. Remission and low disease activity both could thus be considered acceptable treatment targets for anti-CCP negative RA patients, but moderate disease activity results in progression of joint damage and extension of the number of damaged joints. Anti-CCP positive RA patients develop already measureable joint damage progression in low disease activity, and the probability for joint damage occurring in previously undamaged joints is considerable. Remission may be the most appropriate treatment target to prevent occurrence of joint damage progression in that group, according to the EULAR treatment guidelines.[5]

In the current guidelines quick switch to biologics is advised in case of DMARD failure in patients with risk factors for bad prognosis. However, as a consequence of the above the definition of DMARD failure is not equal for all patients and notably dependent on anti-CCP status. The same concept has recently been shown for presence of Rheumoid Factor.[23] The ultimate goal of remission in all RA patients is very hard to achieve in practice and a state of low disease activity is more feasible.[12,13,24] Therefore, if symptoms are acceptable for patients and the risk for joint damage progression is limited, the adapted treatment goal

in the maintenance phase might be low disease activity instead of remission in anti-CCP negative patients.[14] However, before we can generally conclude that in an anti-CCP negative patient with low disease activity the joint damage will not progress, even in the swollen joints, other prognostic baseline factors like high ESR and presence of erosions should be considered. Levels of inflammation that are unlikely to lead to joint damage may very well be unacceptable from the patients point of view or may lead to other deleterious effects, such as the development of atherosclerosis.[25] Therefore, it is important to discuss prognosis as well as patient preferences in the management of RA.

There are also some limitations in our study. The Ratingen score was used to score joint erosions, which is a variation of the Larsen score.[20] The Ratingen score is less used than the Sharp van der Heijde score and therefore harder to interpret for rheumatologists. A difference with the Sharp van der Heijde score is that the Ratingen score regards only erosions and not joint space narrowing (JSN). However, the same joints are evaluated and due to the relative weight given to erosions versus JSN in Sharp van der Heijde score, the Ratingen score and Sharp van der Heijde erosion score are closely correlated.[26-29]

As X-ray readings of over 300 patients of the cohort included until August 2002 were available, we analyzed this subset of the cohort. The amount of joint damage progression in this subset is higher than can be expected from patients that have been diagnosed with RA more recently, because of earlier diagnosis, better treatment and possibly the milder disease course the last years.[30,31] However, the advantage of an older cohort is that the disease course of patients who are less intensively treated is more reflective of the 'natural course'. Patients that are diagnosed more recently have less often joint damage at baseline due to earlier diagnosis. The difference between anti-CCP positive and -negative patients was highest in the subgroup without joint damage at baseline. This is thus especially important in recently diagnosed patients.

There were treatment differences between the anti-CCP negative and anti-CCP positive groups. Regarding DMARD use and glucocorticosteroids use, the anti-CCP positive patients were treated somewhat more intensively. These differences rather lead to underestimation than to overestimation of the differences in X-ray progression that were found.

We observed that anti-CCP negative patients have a lower progression rate for joint damage and a lower probability that previously unaffected joints will be damaged after three years as compared to anti-CCP positive patients. This has implications for clinical treatment and for future research. As a result of the higher 'tolerable' level of disease activity in anti-CCP negative patients less stringent treatment targets could be used in these patients and low disease activity might be an alternative for remission as a target. Further research is

needed to determine the right treatment target for patients with limited risk for progression of joint damage when drug-free remission is not attainable, given the anti-CCP status and other baseline risk factors, and taking into account safety, medical costs, and patient's perceived effect of disease for treatment with DMARDs as well as with biologics.

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Er was eens een stad

waar de mensen niet meer met elkaar spraken

daar hadden ze gewoon geen tijd meer voor

of ze waren het verleerd

het was niet dat ze het zo wilden

maar niemand kon zich voorstellen

dat het nog anders kon

tot er iemand langs kwam die dat niet wist

Fragment uit *Tot dat er iemand langs kwam*.
Theateratelier Rotterdam Zuid - Formaat 2013

A simplified baseline prediction model for joint damage progression in rheumatoid arthritis. A step towards personalized medicine

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Abstract

Objective

To compare the performance of an extended and a simplified prognostic model for joint damage in RA, based on three baseline risk factors: anti-CCP, erosions and acute phase reaction.

Methods

Data were used from the Nijmegen early RA cohort. An extended and a simplified baseline prediction model were developed to predict joint damage progression between 0 and 3 years. Joint damage progression was assessed using the Ratingen score. In the extended model the prediction factors were: positivity for anti-CCP and/or Rheumatoid Factor, the level of ESR and the quantity of erosions. The prediction score was calculated as the sum of the regression coefficients. In the simplified model the prediction factors were dichotomized and the number of risk factors was counted. Performance of both models was compared using discrimination and calibration. The model was internally validated using bootstrapping.

Results

The extended model resulted in a prediction score between 0 and 5,6 with an area under the ROC curve of 0.77 (95% CI 0.72-0.81). The simplified model resulted in a prediction score between 0 and 3. This model had an area under the ROC curve of 0.75 (95%CI 0.70-0.80). In internal validation the two models showed reasonably well agreement between observed and predicted probabilities for joint damage progression (Hosmer-Lemeshow test $p>0.05$ and calibration slope near 1.0).

Conclusion

A simple prediction model for joint damage progression in early RA, by only counting the number of risk factors, has adequate performance. This facilitates the translation of the theoretical prognostic models to daily clinical practice.

Introduction

Rheumatoid Arthritis is a multifactorial disease with joint damage as one of its hallmarks. An important aim in the treatment of RA therefore is prevention of joint damage, next to relieving symptoms and prevention of disability. It is common knowledge that the risk for joint damage is not the same for all RA patients and in the current treatment guidelines it is advised to take the risk for this unfavourable prognosis into account.[1,2] Three prognostic factors are regarded as most strongly determining the probability of joint damage progression in early RA: presence of anti-cyclic citrullinated peptide (anti-CCP) and/or Rheumatoid factor (RF), presence of erosions and high levels of acute phase response. In case of persistent high or moderate disease activity due to MTX failure, patients with one of these three main factors for unfavourable prognosis at diagnosis are advised to switch to biologics earlier as compared to patients who do not have these risk factors.[1,2] Moreover, making use of the window of opportunity in the treatment of RA it is suggested that patients with a high risk for joint damage progression should already at the moment that RA is diagnosed be treated with more intensive therapy, like methotrexate with a high dose of prednisone, combination therapy with 2 or 3 DMARD's or even biologics.[3,4]

To guide this treatment strategy for an individual patient several multivariable prognostic models have been developed to predict the risk for joint damage progression in early RA.[5,6] Interestingly, the models agree about the factors that are important for the prognosis: anti-CCP, high acute phase reactant and presence of erosions. However, the importance of the three risk factors and their weight in the prediction models varies considerably between the models. Until now, none of the prediction models appears to be widely used in daily clinical practice for estimation of the risk for joint damage progression and personalization of the treatment. Probably this is because the translation from the regression coefficients or Odds Ratios in the prediction models to a clinically useful risk estimation for the individual patient is not often made. In the last few years matrices have been developed for use in daily clinical practice.[7-10] However, in external validation discriminative ability of these models appeared to be disappointing.[11,12]

We hypothesized that further simplification of the prediction models could increase generalizability and could facilitate the translation from the theoretical prediction model for use in daily clinical practice. For this reason we aimed to develop a simplified prediction model for the prediction of the risk for joint damage progression in early RA. Simplification is only useful if it doesn't result in a significant loss of predictive performance. Therefore, the objective of this study was to compare the performance of an extended and a simplified baseline prognostic model for joint damage in RA, based on anti-CCP, erosions and acute phase reaction.

Methods

Design

Data of the first three years of disease were used from patients of the Nijmegen early RA inception cohort, who were included from 1985 until 2008.[13] All patients provided written informed consent. In the Netherlands no formal approval of a Medical Ethical Review Board is necessary for this kind of observational studies.

Patients

RA-patients were consecutively included in the cohort if they fulfilled the 1987 ACR criteria for RA, had a disease duration less than one year, had no prior DMARD use, and were aged 18 years or older. There were no exclusion criteria.[13] Cohort patients were included for the current analyses if X-rays were available at inclusion and after two or three years of follow up. Patients that were treated with biologic DMARD's within the first three years of disease were excluded from the analyses because this kind of medication may modify the relation between inflammation and joint damage progression.[14]

Assessments

At diagnosis clinical data were collected including presence of anti cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), shared epitope (SE), and smoking status (ever or never smoker). The level of inflammation at baseline was assessed using Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen joint count of 44 (SJC) and 28 joints (SJC28), tender joint count of 53 (TJC) and 28 joints (TJC28), VAS General Health (GH), and VAS Pain.

X-rays of hands and feet were taken at baseline, 1, 2 and 3 years follow up. X-rays at baseline and 3 years follow up were scored according to the Ratingen score.[15] This is a modification of the Larsen score, evaluating the percentage of joint surface destruction of 38 joints of hands and feet, graded from 0 to 5 (range 0-190). Joint damage progresses most in the first three years of the disease.[16] Therefore the change in Ratingen score between baseline and 3 years was the outcome of the prediction model. A subset of X-rays had been read in 2002 by four raters (ICC 0.85). For this study X-rays from 2002 until 2011 were read by 2 raters (ICC 0.95). Joint damage progression was defined as a difference of ≥ 5 Ratingen points between baseline and 36 months follow up, corresponding with the smallest detectable change (SDC) in this cohort, as previously calculated.[17] Sensitivity analyses were done with ≥ 1 and ≥ 10 Ratingen points as the cut point for joint damage progression.

Analyses

First it was checked whether the main baseline prognostic factors for joint damage progression in RA as mentioned in literature, anti-CCP, ESR and erosions, were also the main prognostic factors for joint damage progression in our cohort. The association with joint damage progression in the first three years of the disease was analyzed using univariable and multivariable logistic regression with the potential predictors: smoking status (ever smoked/ never smoked), anti-CCP and RF combined (0, 1 or 2 positive), SE (positive / negative), SJC28 (0-5 / 6-10 / 11-15 / > 15), TJC28 (0-5 / 6-10 / 11-15 / > 15), DAS28 (≤ 3.2 / 3.3-5.1 / ≥ 5.2), CRP (≤ 5 / 6-10 / ≥ 11), ESR (< 25 / 25-50 / > 50 mm/h), VAS pain (0-29 / 30-60 / 61-100), GH (0-29 / 30-60 / 61-100) and erosions at baseline (0 / 1-5 / 6-10 / > 10 Ratingen points). In the multivariable model using backward selection with $p < 0.20$ as the selection criterion, it appeared that anti-CCP, ESR and erosions were strongly and significantly associated with joint damage progression. SJC28 was significantly but weakly associated with joint damage progression. Therefore, further analyses were done with the three main risk factors as known from literature and without SJC28. Age (< 45 / 45-60 / > 60 years old at diagnosis) and sex were added to the model to be able to apply the model regardless of sex and age.

Subsequently two baseline prediction models were made, including anti-CCP, ESR and erosions as the prognostic factors and also including age at diagnosis and sex. The first model was an extended model, in which prediction factors at baseline were categorized: positivity for anti-CCP and/or RF (positive for 0, 1 or 2, with anti-CCP > 25 U/ml regarded positive, anti-CCP > 10 U/l regarded positive in the subset (37%) of post hoc frozen samples, and >10 U/ml as the cut point for RF); the level of ESR (< 25 / 26-50 / > 50 mm/h); and the amount of erosions (0 / 1-5 / 6-10 / > 10 Ratingen points). [Anti-CCP was measured using ELISA immunoscan RA Mark 2, Euro Diagnostica, Malmo Sweden and for the post hoc frozen samples EliA-CCP, Thermo scientific, Uppsala, Sweden]. The prediction score for joint damage progression was defined as the sum of the regression coefficients of the three predictors in the multivariable regression model.[18] The second model was a simplified model in which the three prediction factors were dichotomized: anti-CCP > 25 U/ml (> 10 U/l in the post hoc frozen samples), ESR was considered high if > 25 mm/h, and Ratingen score at baseline ≥ 1 was considered as erosiveness. The prediction score for joint damage progression was defined as the number of prognostic factors present (0-3).

Missing values analysis was performed by evaluating the frequencies and patterns of missing variables, using SPSS' missing value analysis. Missing values showed no recognizable pattern and were considered missing at random. Missing X-rays at 3 years follow up were imputed using the X-rays at 2 years follow up, according to the last observation carried

forward principle. Missings of the prediction variables were imputed using multiple imputations with 5 imputed data sets, based on the continuous baseline variables ESR, CRP, SJC28, TJC28, VAS pain, GH, age, Ratingen score and the categorical variables smoking status, sex, RF, anti-CCP, shared epitope, and erosions at 3 years follow up.

Internal validation was performed using a bootstrapping procedure with 300 repetitions as usual, for every of the 5 imputed data sets separately.[19,20] Performance of the extended and simplified models was assessed by calculating discrimination and calibration. The discriminative ability was calculated as the area under the receiver operating characteristic-curve (ROC-curve). Goodness of fit was tested using the Hosmer-Lemeshow test in which a p-value < 0.05 indicates lack of fit, and using the calibration slope. A calibration slope of 1.0 means that (in the bootstrap samples) the prediction rule agrees well with the observations. Results for discrimination and calibration of the 5 imputed datasets were combined according to Rubin's rules or given as ranges, as appropriate.[20,21] Statistical Package for Social Sciences (SPSS) version 20.0 (Chicago, Ill) and Statistical Analysis System (SAS) version 9.2 (North Carolina) were used for the analyses.

Results

Patients

Until December 2008, 607 patients were included in the Nijmegen early RA cohort at the Radboud University Medical Centre. 77 patients (13%) were lost to follow up during the first three years of disease (2% moved, 2% died, 1% stopped because of comorbidity, 5% did not want to participate anymore, 2% had no RA after all, 1% got lost for unknown reason). For 90 patients (15%) no X-rays of hand and feet were available at 2 or 3 years follow up. Fifteen patients were excluded because of treatment with biologic DMARD's during the first three years of disease. Anti-CCP was missing in 54 (13%) patients and ESR at baseline in 19 (4%) patients of the study population. Missings of baseline variables were overcome by multiple imputation and therefore data of 425 (70%) patients could be used for the analyses. X-ray score at 3 years follow up was imputed in 12% of patients.

Baseline

In table 1 baseline data of the patients with and without joint damage are presented. Of the 425 patients 175 (41%) had progression of joint damage between 0 and 36 months and 250 had no progression. The patients in the group *with* joint damage progression had a mean age of 54 years (SD 14) and 59% was female. Of these patients 82% was positive for anti-CCP, 62% had erosions at baseline and the median ESR at baseline was 40 mm/h. The patients in

the group *without* joint damage had a mean age of 57 years (SD 14) and 66% was female. Of these patients 53% was anti-CCP positive, 32% had erosions at baseline and the median ESR was 21 mm/h. Anti-CCP positivity, RF positivity, baseline inflammation levels and presence of erosive lesions on x-rays at baseline were significantly higher in the group of patients *with* joint damage progression. These patients were also significantly younger than the patients *without* joint damage.

	Joint damage progression		No joint damage progression		p-value
	N	Mean/med/%	N	Mean/med/%	
Age (yrs)	175	54 (14)	250	57 (14)	0.029
Female	175	59% (104)	250	66% (165)	0.167
Anti-CCP positive	158	82% (129)	213	53% (112)	< 0.001
RF positive	175	87% (153)	246	66% (163)	< 0.001
SE present	164	75% (123)	188	68% (128)	0.153
Smoking (ever)	131	72% (94)	176	67% (118)	0.377
DAS28	170	5.5 (1.3)	241	4.9 (1.4)	< 0.001
ESR mm/h	168	40 [21-59]	238	21 [9-38]	< 0.001
CRP mg/l	118	22 [7-52]	206	3 [0-23]	< 0.001
SJC28	173	11 [7-16]	244	10 [6-14]	0.017
SJC	142	15 [10-22]	153	13 [9-19]	0.041
TJC28	173	7 [4-13]	244	6 [2-12]	0.070
TJC	142	13 [6-19]	153	12 [5-19]	0.269
VAS pain (0-100)	157	47 [28-60]	228	47 [31-64]	0.241
Erosions at BL	175	62% (108)	250	32% (80)	< 0.001
Ratingen Score	175	2 [0-4]	250	0 [0-1]	< 0.001
DMARD combination	175	21% (37)	250	20% (51)	0.253
monotherapy		75%(132)		72% (181)	
Oral prednisone	175	25% (44)	250	15% (38)	0.013

Table 1. Baseline and medication use of study population *(unimputed data)*, stratified by occurrence of joint damage progression between 0 and 3 years. Values are mean (SD), % (number) or median [P25-P75]. Joint damage progression was defined as ≥ 5 Ratingen points. Anti-CCP = anti-cyclic citrullinated peptide, RF = Rheumatoid Factor, DAS28 = disease activity score 28 joints, ESR = erythrocyte sedimentation rate, CRP = c-reactive protein, SJC28 = swollen joint count 28 joints, SJC = swollen joint count 44 joints, TJC28 = tender joint count 28 joints, TJC = tender joint count 53 joints, VAS pain = pain measured on a visual analogue scale. Treatment with synthetic DMARD's and oral prednisone was evaluated between 0 and 36 months. Statistic tests used were unpaired t-test, Chi square test and Mann Whitney U test, as appropriate.

Of the patients *with* joint damage progression 75% was treated with DMARD monotherapy and 21% with DMARD combination therapy between 0 and 36 months follow up. Oral prednisone was used by 25%. Of the patients *without* joint damage progression 72% and 20% used monotherapy and combination DMARD therapy respectively and 15% of patients was treated with oral prednisone. Use of oral prednisone was significantly lower in the group without joint damage progression (p = 0.013). Other differences in treatment between the two groups were not significant.

Extended prediction model: Categories of the three risk factors

All three prognostic variables, anti-CCP/RF, ESR and presence of erosions, were univariably and multivariably significantly associated with joint damage progression (table 2). The sum of the regression coefficients resulted in a prediction score with a range between 0 and 5.6. The median prediction score for the patients *with* joint damage progression was 3.0 [IQR 2.1-3.7], as compared to 1.3 [IQR 1.0-2.3] in patients *without* joint damage progression ($p < 0.001$). A patient that is anti-CCP and RF positive with low ESR and no erosions at baseline would have a prediction score of 1.34, corresponding with a predicted probability for joint damage progression of 0,25. A patient that is anti-CCP and RF positive with high ESR and no erosions at baseline, would have a prediction score of 2.95, corresponding with a predicted probability of 0,62 (figure 1A). Usually, an (online) calculator is used for this purpose in the clinic. The prediction model had an area under the ROC-curve of 0.77 (95% CI 0.72-0.81) (figure 2). Sensitivity analyzes with 1 and 10 as cut points for joint damage progression showed a similar AUC.

Internal validation was applied using bootstrap samples. The shrinkage factor (95% CI) was 0.90 (0.88-0.92). The discrimination according to the area under the ROC curve changed little and ranged from 0.76-0.77. Agreement between predicted and observed probabilities (calibration) as reflected by the Hosmer Lemeshow test was adequate in all five imputed datasets with p-values ranging between 0.41 and 0.85. The calibration slope (95% CI) was 1.0 (0.82-1.21).

Simplified prediction model: Dichotomisation of the three risk factors

In the simplified prediction model anti-CCP positivity, high ESR and erosions at baseline were univariably and multivariably significantly associated with joint damage progression. The prediction score of the simplified model represented the number of unfavorable prognostic factors present in a patient (0 - 3) (table 3). 2% of patients *with* joint damage progression had 0 risk factors, 19% had 1 risk factor, 40% had 2 and 39% had 3 risk factors.

		ß	OR	95% CI OR	p-value
Anti-CCP/ RF	0	--	--	--	--
	1	0.19	1.20	0.52-2.79	0. 666
	2	1.34	3.80	1.92-7.50	< 0.001
Erosions	0	--	--	--	--
	1-5	0.95	2.57	1.57-4.23	< 0.001
	5-10	1.35	3.87	1.68-8.95	0.002
	> 10	2.61	13.55	3.34-54.99	< 0.001
ESR	< 25	--	--	--	--
	25-50	0.99	2.69	1.58-4.59	< 0.001
	> 50	1.61	4.98	2.67-9.29	< 0.001
Age	< 45	--	--	--	--
	45-64	-0.18	0.84	0.47-1.48	0.539
	> 64	-0.89	0.41	0.21-9.81	0.010
Sex	female	-0.45	0.64	0.40-1.03	0.065
Constant		-1.43	0.24	0.08-0.75	0.014

Table 2. Extended multivariable logistic regression model for the prediction of joint damage progression between 0 and 36 months follow up, with the baseline variables presence of anti-CCP and/or RF, erosiveness according to the Ratingen score and ESR (mm/h). The model was corrected for age and sex.

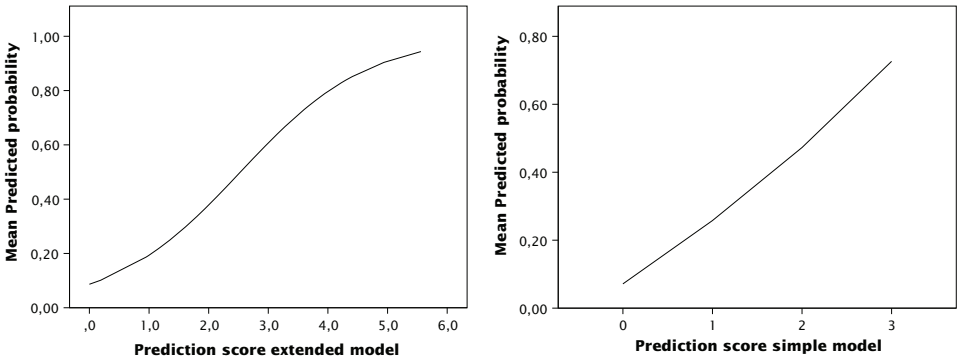

Figure 1. Predicted probability for joint damage progression for two different prediction scores. **A**. Prediction score based on the regression coefficients in the extended model. **B**. Prediction score based on the number of prediction factors according to the simplified model.

In the group of patients *without* joint damage progression 21%, 38%, 31% and 10% of patients had 0, 1, 2 and 3 risk factors respectively ($p < 0.001$). The number of risk factors present, 0, 1, 2 and 3 corresponded with a probability for joint damage progression of 0.09, 0.25, 0.49 and 0.57 respectively. (figure 1b) The discriminative ability of the simplified model, as was calculated by the area under the ROC-curve of 0.75 (95% CI 0.70-0.80) was moderate good (figure 2). Sensitivity analyzes with the cut points 1 and 10 resulted in the same AUC.

In the internal validation procedure the shrinkage factor (95% CI) was 0.98 (0.96-1.0). Discrimination according to the area under the ROC curve ranged from 0.75 to 0.76. Calibration was adequate with p-values of the Hosmer-Lemeshow test varying between 0.87 and 0.99. The calibration slope (95% CI) was 1.1 (0.89-1.33).

		n	ß	OR	95% CI	p-value
Number of riskfactors	0	56	--	--	--	--
	1	128	1.36	3.91	1.26-12.09	0.018
	2	146	2.93	10.95	3.70-32.40	< 0.001
	3	95	3.61	37.01	11.74-116.6	< 0.001
Age	< 45		--	--	--	--
	45-64		-0.23	0.79	0.45-1.39	0.415
	> 64		-0.77	0.46	0.25-0.86	0.015
Sex	female		-0.40	0.70	0.42-1.06	0.085
Constant			-1.53	0.22	0.06-0.85	0.028

Table 3. Simplified multivariable logistic regression model based on the number of baseline risk factors present. The three baseline prognostic factors were anti-CCP positivity > 25 U/ml, high ESR > 25 mm/h and presence of ≥ 1 erosions. The model was corrected for age and sex.

Discussion

The objective of this study was to compare the performance of an extended and a simplified prediction model for joint damage progression based on the baseline prediction factors anti-CCP, high ESR and erosions. The extended model resulted in a prediction score varying between 0 and 5.6, with adequate discrimination and calibration. The simplified model resulted in a prediction score from 0 to 3, also with adequate discrimination and calibration. The discriminative ability of the simplified model was comparable to the extended model. In internal validation it was seen that especially the predictions of the simplified model were

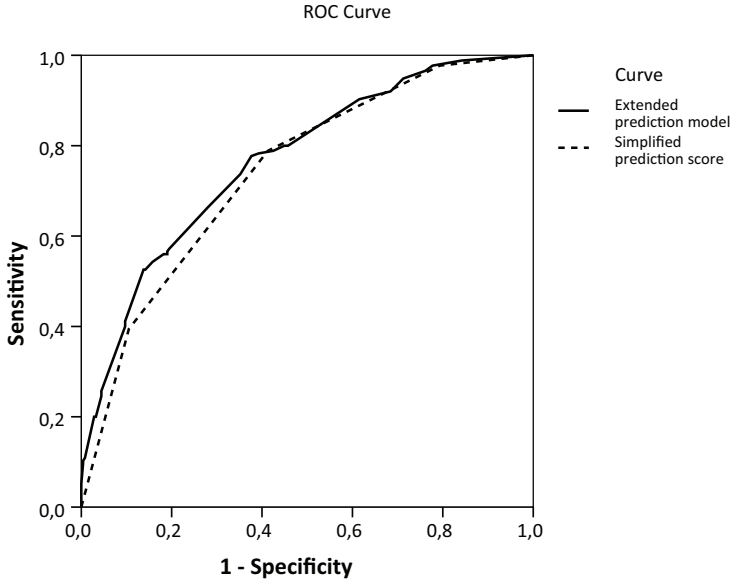

Figure 2. Discriminative ability of the extended and simplified prediction model for joint damage progression between 0 and 36 months presented as the area under the ROC-curves. Areas under the ROC curve were 0.77 (95% CI 0.72-0.81) and 0.75 (95% CI 0.70-0.80) for the extended and simplified model respectively. In the extended model anti-CCP, ESR and erosions are categorized and in the simplified model the prediction factors are dichotomized.

robust. There was virtually no overoptimism (shrinkage factor 0.98) and the discrimination remained unchanged (area under the ROC curve 0.75). It is generally known that having more risk factors is associated with a higher risk of progression. The value of this kind of models is that it gives insight in the exact probability.

Identification of the main prognostic factors for joint damage progression in RA has been done in several studies. Translation of the prognostic factors into a clinically useful prediction model has also been done in other studies by quantifying the risk for joint damage progression for different risk groups. Vissers model resulted in 9 groups by categorization of CRP, the amount of erosions and positivity for anti-CCP and/or RF.[7] Fautrel divided the study population in 36 groups by categorization of CRP, erosions, anti-CCP and SJC28.[8] The simplification of our model resulted in quantification of the risk for 4 risk groups. Performance of the model of Visser and Fautrel in our data was in the range of the models developed in our study with discriminative abilities in the range from 0.76 to 0.79.

Simplification of a prediction model might be paid for with loss of performance, regarding discriminative and predictive ability. This was also true for our simplified prediction model, although not statistically significant. When performance of the models is similar a simple model is easier to use in the clinic. Whether or not these values are acceptable depends on the consequences of the intended therapy. Misclassification is more worrisome if a therapy is expensive, burdensome or highly toxic.

The starting point of our analyzes was to find out how to use the prognostic factors anti-CCP, ESR and erosiveness in a simplified baseline prediction model that could facilitate the translation of the theoretical models for use in daily practice. Univariable and multivariable logistic regression analyses confirmed these three factors as the most important prognostic factors for joint damage progression. Because the regression coefficients for these three variables were about equal, equal importance of the predictors is suggested. SJC28 was significantly but weakly associated in the multivariable model. Therefore we decided not to use this predictor in further development of the simple model. Because age and sex were added as confounders to both models, the prediction scores are independent of age and sex.

In textbooks and guidelines it is suggested that RA patients with an unfavourable prognosis regarding joint damage progression should be treated differently from patients with a better prognosis.[1,2] Commonly, anti-CCP, RF, erosions and a high level of acute phase reactant are regarded as factors pointing to an unfavourable prognosis. At the same time, the exact risk for joint damage progression remains unclear. The results of this study showed how the three main baseline predictive factors can be translated into a simple risk model for joint damage progression in early RA without loss of predictive performance.

A prediction score extracted from the extended model can guide treatment choices in daily practice by setting cut points on the continuous scale of the prediction score. In general three categories can be extracted from the S-curve of a prediction model: a save range at low scores in which patients can be treated with less intensive treatment, an unsafe range at high scores asking for an intensive treatment strategy, and third an intermediate category in which additional prognostic tests are valuable or close follow up is needed so that treatment can be intensified quickly if remission or low disease activity is not reached quickly. Easier than scoring the prognostic factors is to count them. According to the results of this study this could result in four risk categories. The next step for translation into clinical practice is to study the optimal treatment strategy for each of these four categories. This is a step towards personalized medicine in RA.

Next to baseline factors, the level of disease activity over time is also important for estimation of the risk for joint damage progression. A direct consequence could be to define

different treatment targets for disease activity for each of the 4 risk categories.[22]

Regularly new possible prediction factors for joint damage in RA are identified, like Power Doppler of an index joint or anaemia.[23-25] Future research could focus on the additive value of these newly identified prediction factors in a multivariable regression model with anti-CCP, erosiveness and ESR at baseline. However, before further development of the simplified baseline prediction model we recommend that this model is externally validated in other early RA samples to verify the equal importance of the three main risk factors for the prediction of joint damage progression.

Deliberately, an old RA cohort was used for the development of the models with an inclusion period from 1985 until 2008. This might be seen as a limitation of the study, but that is not the case per se. Patients in our cohort had more joint damage than can be expected in a more recent cohort due to earlier diagnosis, more intensive treatment and a milder disease course the last years.[26] Ideally, prognostic models are developed in patients who are untreated, ie. follow the natural course of disease. The advantage of an old cohort that it is less intensively treated is that it resembles the natural course of RA as close as possible.

The Ratingen score was used for evaluation of joint damage, which is a variation on the Larsen score. Differences between the Ratingen score and the more often used modified Sharp score (mSharp) are that in the Ratingen score the percentage of destructed joint surface is scored rather than the number of erosions, and that joint space narrowing is not scored. However, in the Ratingen score and mSharp score the same joints are evaluated and the two scores are closely correlated.[27,28]

In conclusion, a simplified prediction model for joint damage progression in early RA only counting the number of risk factors anti-CCP, high ESR and erosions, has adequate discriminative ability and has similar predictive performance as compared to an extended model based on the same variables. A simplified model facilitates the translation from a theoretical model to daily clinical practice and further differentiates in the current dichotomy in treatment guidelines, being at risk or not being at risk for unfavourable prognosis. This can guide treatment choices and is a step towards personalized medicine in RA.

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patiëntenzorg | *zorg voor de patiënt* | de zorg voor de patiënt | *hoe jij zorgt voor die patiënt* | hoe ik de zorgen over neem van de patiënt | *hoe jij het leven leeft* | van de patiënt? | *nou ja, hoe jij de regie voert* | over het leven? | *over de patiënt* | die ziek is | *die ziek is* | Dat is natuurlijk een belangrijk verschil | *met?* | gewone mensen | *precies* | Want uiteindelijk ben ik vooral expert van de ziekte | *en niet expert van het leven* | dat is de patiënt zelf | *tuurlijk, als het over zijn eigen leven gaat wel* | ik ga over de ziekte | *niet over zijn leven* | nee? | *nou ja, dat denk ik* | dus ik zorg ervoor | *jij neemt alle zorgen over* | ik neem | *jij neemt* | ik denk | *jij denkt* | ik bepaal | *jij bepaalt* | ik denk dat ik het goed doe | *jij doet het goed* | hoe weet je dat?

Fragment uit *De limonadefabriek*, Theatergroep Plezant 2011

Personalizing treatment targets in rheumatoid arthritis by using a simple prediction model

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5

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Abstract

Objective

To develop a personalized treatment target approach in patients with RA, based on baseline risk factors for joint damage progression in combination with disease activity over time.

Methods

Data were used from the Nijmegen Early RA cohort. Presence or absence of anti-CCP, high ESR and erosions was translated into four risk profiles. Joint damage progression was assessed with the Ratingen score and disease activity with the original Disease Activity Score (DAS) over 3 years. The probability for joint damage progression was calculated for each risk profile and each DAS category, using logistic regression models. The probabilities were translated into personalized disease activity treatment targets.

Results

More risk factors at baseline as well as a higher DAS level resulted in a higher probability for joint damage progression in a dose dependent way. Low DAS corresponded with a probability of 0.0, 0.08, 0.20 and 0.58 in patients with 0, 1, 2 and 3 risk factors respectively. Moderate DAS corresponded with a probability of 0.06 in patients with 0 risk factors and 0.35 with 1 risk factor. High DAS resulted in a probability of 0.50 already with no risk factors present at baseline.

Conclusion

Presence of anti-CCP, acute phase response and erosiveness at baseline can be used to set individual treatment targets in RA. In patients without these risk factors a moderate DAS as a target is sufficient, while for patients with all three risk factors a low DAS is not even strict enough to limit the risk for joint damage.

Introduction

The treat-to-target approach in the treatment of Rheumatoid Arthritis (RA) has shown to be beneficial in clinical trials as well as in clinical practice.[1-4] Remission or low disease activity is commonly used as the target in a treat-to-target approach, because generally more disease activity leads to more joint damage progression, especially in the first three years of disease.[5] The exact treatment target differs in studies and between guidelines.[3,6,7] However, commonly patient characteristics are not taken into account: a 'one size fits all' treatment target, such as DAS<1.6 or DAS28 < 2.6, is used for all RA patients. Although drug-free remission is the ultimate treatment target for all patients, this is infrequently reached yet.[8]

The relation between disease activity and joint damage progression is strongly modified by presence of Rheumatoid Factor and anti-CCP.[9,10] There is evidence that anti-CCP positive RA patients have joint damage progression at lower levels of disease activity than anti-CCP negative patients.[10] This idea is in line with observations of many rheumatologists in clinical practice. Consequently, it can be conceived that if the aim is to prevent joint damage progression, the treatment target can be personalized using baseline risk factors. Then, not all synovitis needs to be repressed in patients with a low risk for joint damage progression while for patients with a high risk for joint damage progression, no residual synovitis can be accepted.

Another reason for personalization of treatment targets is that the Patient Acceptable Symptom State is often at the level of low or moderate disease activity.[11,12] At the same time, guidelines prescribe remission as the ultimate goal in all RA patients and current treatment targets do not regard these individual patient preferences.[6,7] If a patient is satisfied with a certain level of inflammation and the rheumatologist could reliably estimate that the risk for joint damage progression is limited, there probably is no good reason to strive for remission for that individual patient at all costs. It is desirable to make a step towards personalized medicine and differentiate in the 'one-size-fits-all' treatment target, based on the individual risk for joint damage progression and patient preferences. It should be clear that with the progress in effective and affordable treatment options, treatment targets should and will shift in the future.

Several prognostic models have been developed to estimate the individual risk for joint damage progression.[13-17] These models agree in the importance of three baseline factors for prediction of worse prognosis regarding joint damage progression: presence of anti-CCP, high level of ESR and presence of erosions. Especially the matrix models seem to be practical for use in daily practice.[18-21] However, none of these matrix models are currently widely used in daily practice. A reason might be that the models are based on baseline factors and that the most important dynamic prognostic factor, disease activity over time, is not included in these

models. Therefore, the objectives of this study were to combine baseline risk factors with disease activity over time and to show how this can be used to derive personalized treatment targets for disease activity in RA, with the scope to prevent joint damage progression in the first three years of disease.

Methods

Design

Data were extracted from the Nijmegen Early RA cohort of the Radboud University Medical Centre in Nijmegen, The Netherlands. In this old cohort that started in 1985 patients were not as intensively treated as nowadays. Data of the first three years of the disease were used of the patients included before December 2008.[22] All patients provided written informed consent to be included in the cohort. No additional formal approval of a Medical Ethical Committee had to be obtained, because this is not required in the Netherlands for this kind of observational studies.

Patients

Patients were consecutively included in the early RA cohort if they fulfilled the 1987 ACR criteria for RA, had a disease duration less than one year, had no prior use of DMARDs and were aged 18 years or older. Cohort patients were included for the current analyses if X-rays of hands and feet were available at baseline and at two or three years follow-up, and if patients had at least 4 visits with assessment of the original DAS (Disease Activity Score).[23] The maximum accepted interval between two visits was one year. Patients treated with biological DMARDs during the first three years were excluded from the current study, because this type of medication changes the relation between disease activity and joint damage.[24,25]

Assessments

Demographics, smoking status, shared epitope and disease activity were standardly assessed. Disease activity was assessed at baseline and every three months, including Swollen Joint Count of 44 joints (SJC), Tender Joint Count of 53 joints (TJC), Ritchie Articular Index (RAI), Erythrocyte Sedimentation Rate (ESR) and General Health (VAS GH), so that the original DAS could be calculated.[23] In the analyses, instead of the mean DAS, the 80th percentile of the DAS's between 6 and 36 months for each individual patient was used. This means that after the initial decrease of the DAS in the first 6 months of treatment, 80% of the DAS's of an individual patient were at or below this level between 6 and 36 months. Sensitivity analyses were done with the median and maximum DAS. DAS-scores were classified according to the known DAS-cut points: low DAS (< 2.4), moderate DAS (2.4-3.7) and high DAS (> 3.7).

X-rays of hands and feet were taken at baseline, 1, 2 and 3 years follow up. X-rays at baseline and 3 years follow up were scored according to the Ratingen erosion score.[26] This is a modification of the Larsen score, evaluating the percentage of joint surface destruction, graded from 0 to 5 (range 0-190). Progression of joint damage progression was defined as a difference of > 5 Ratingen points. This was based on the smallest detectable change (SDC) in our cohort, as previously calculated.[27] A subset of X-rays had been read in 2002 by four raters (ICC 0.85). For this study X-rays from 2002 until 2011 were read by two raters (ICC 0.95)

Baseline risk factors

A baseline prediction model for joint damage progression between 0 and 36 months was previously developed.[28] In this model anti-CCP, Rheumatoid Factor, Shared Epitope, SJC28, TJC28, ESR, VAS pain, VAS general health, erosions at baseline and smoking status were included as possible predictors for joint damage. A multivariable model using backward selection showed that anti-CCP, ESR and erosiveness at baseline were strongly and significantly associated with joint damage progression. An extended model with categorization of these three factors was compared to a simplified model in which the three prediction factors were dichotomized. The cut points chosen in the simplified model were anti-CCP > 25 U/l (ELISA immunmoscan RA Mark 2, Euro Diagnostica, Malmo, Sweden) and > 10 U/l for the post hoc evaluated samples with fluoroenzymeimmunoessay (EliA-CCP, Thermo scientific, Uppsala, Sweden), ESR > 25 mm/h was considered high (60 minute Westergren mode, StaRRsed Compact InteRRliner V8, Mechatronics, Etten-Leur The Netherlands) and for presence of erosions at baseline the cut point was ≥ 1 Ratingen point. Both the extended and the simplified model had moderate good discriminative ability (area under the ROC curve 0.77 and 0.75 respectively) and adequate calibration. Because the simplified model was more user-friendly for daily practice, the simplified model was used in this study. Four risk profiles were defined based on presence or absence of the three main baseline risk factors for joint damage progression in the simplified baseline model: anti-CCP positivity, high ESR and presence of erosions. The risk groups 0, 1, 2 and 3 represented the number of risk factors present in the individual patient.

Analyses

Patient characteristics at baseline and follow up were evaluated separately for the 4 risk groups. Differences between the groups were analyzed with one-way ANOVA, Chi-square test and Kruskal Wallis test, as appropriate. The difference in joint damage progression between the risk groups was analyzed in two ways, i.e. the probability for progression and

the amount of progression, both between 0 and 36 months. Next, patients were categorized by the number of baseline risk factors and the level of the DAS over time (80th percentile): low (< 2.4), moderate (2.4-3.7) and high (> 3.7). The probability for joint damage progression was analyzed for each category of disease activity and for all 4 risk groups separately, using logistic regression models. Finally, the probabilities for joint damage progression were translated into DAS treatment targets for each risk profile with the aim to limit the risk for joint damage progression.

Missing values analysis of the DAS-variables was performed by evaluating the frequencies and patterns of missing variables, using SPSS' missing value analysis. Missing values showed no recognizable pattern and were considered being missing at random. Missing visits were interpolated by calculating the average DAS of the closest visits before and after the missing DAS, taking into account the distance to the previous and following visit, with a maximum of six months. The number of DAS was completed to 11 for each patient. Missing Ratingen scores at 3 years follow up, were imputed according to the Last-observation-carried-forward principle, with the limitation that the X-ray was taken between 24 and 36 months follow up. Statistics Package for Social Science version 20.0 was used for all analyses.

Results

Until December 2008 607 patients were included in the cohort, 435 (72%) of the cohort patients had X-rays of 0 and 3 years available. 362 (60%) of the patients had at least 4 visits with a maximum interval of 1 year. At all visits DAS28 was assessed, but only in 320 (53%) of the patients DAS was assessed, which was needed for the analyses. Anti-CCP and ESR at baseline were available for 269 (44%) of the cohort patients. Nine Patients had used biologic DMARDs in the first three years of the disease and were excluded, so that finally 260 (43%) patients could be included for analyses. Cohort patients that were excluded from the study did not differ significantly or relevantly from the patients included in the study (not shown). The median number of visits was 9,5 [IQR 8-11] and 29% of the DAS-scores was imputed. 12% (31) of the 260 patients had 0 risk factors, 30% (79) had 1 risk factor (40 x anti-CCP, 26 x ESR, 13 x erosions), 33% (86) had 2 risk factors (43 x anti-CCP and ESR, 27 x anti-CCP and erosions, 16 x ESR and erosions), and 25% (64) of the patients had all 3 risk factors.

With an accumulation of risk factors, patients were more often positive for Rheumatoid Factor and Shared Epitope. DAS and SJC at baseline were also significantly higher in patients with an accumulation of risk factors (Table 1). The percentage of patients with joint damage progression between 0 and 36 months was 10% in patients with 0 risk factors, 25% in patients with 1 risk factor, 58% in patients with 2 risk factors and 80% in patients with 3 risk

Risk factors	0 (n=31)	1 (n=79)	2 (n=86)	3 (n=64)	p-value
Age (years)	56 (14)	54 (14)	55 (14)	54 (14)	0.851
Sex (% female)	61% (19/31)	63% (50/79)	55% (47/86)	61% (39/64)	0.704
Rheumatoid factor	19% (6/31)	71% (56/79)	88% (76/86)	91% (58/64)	< 0.001
Smoking	58% (14/24)	64% (39/61)	74% (49/66)	69% (35/51)	0.445
Shared epitope	52% (14/27)	71% (49/69)	80% (63/79)	70% (42/60)	0.050
DAS	3.5 (1.1)	3.6 (1.3)	4.0 (1.1)	4.6 (0.9)	< 0.001
SJC	12 [10-19]	13 [9-18]	13 [9-20]	18 [13-23]	0.001
TJC	13 [7-19]	12 [6-19]	11 [6-20]	13 [7-22]	0.605
VAS GH	49 (26)	44 (24)	44 (24)	43 (23)	0.706
Number of visits	9 [8-10]	9 [7-11]	10 [8-11]	10 [8-12]	0.276
Anti-CCP positive	0% (0)	51% (40)	81% (70)	100% (64)	
ESR > 25 mm/h	0% (0)	33% (26)	67% (59)	100% (64)	
erosions	0% (0)	17% (13)	50% (43)	100% (64)	

Table 1. Baseline of patients in the study population, by number of risk factors. The number of baseline risk factors regards presence of anti-CCP > 25 U/l, ESR > 25 mm/h and/or erosions ≥1 Ratingen point. DAS = disease activity score, SJC = swollen joint count (44 joints), TJC = tender joint count (53 joints), VAS GH = general health. Variables are presented as percentage (n), mean (sd) or median [IQR]. Statistic tests were Chi-square test, one-way ANOVA and Kruskal-Wallis test as appropriate.

factors ($p < 0.001$) (figure 1A). The amount of progression between 0 and 36 months was also increasing with an increasing number of risk factors present at baseline (figure 1B) ($p < 0.001$).

Patients in the cohort were treated with synthetic DMARD therapy, 83% got DMARD monotherapy and 13% combination therapy (68% mtx and sulfasalazine, 18% sulfasalazine and hydroxychloroquine, 14% other combinations). 40% of patients used MTX, with 10 mg (3,8) as the mean dose (SD); 19% of the study population used oral prednisone and 8% (n=21) used ≥ 15 mg daily during the first three years of disease. Treatment changed over time. None of the patients was treated with biologic DMARDs, because this was an exclusion criterion. There were only small differences in treatment between the 4 different risk profiles (table 2).

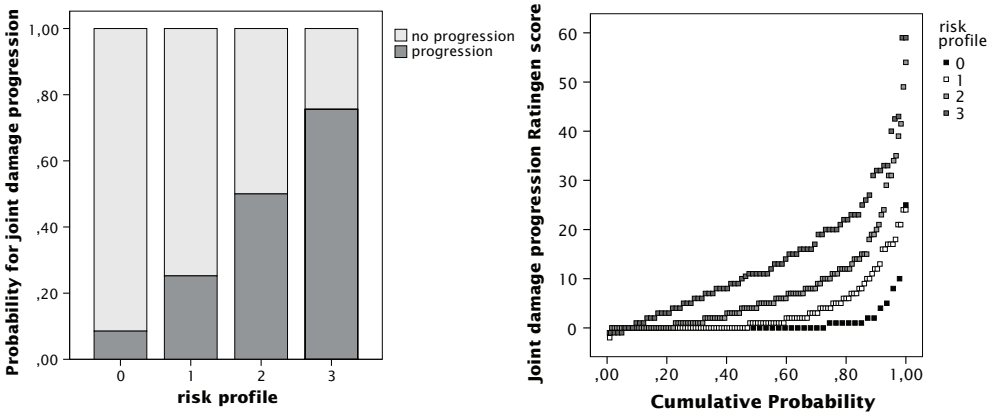

Figure 1. Joint damage progression by number of risk factors. **A**. Number of patients with and without joint damage progression between 0 and 36 months, with Ratingen ≥ 5 points as cut point. **B**. Cumulative probability plot of joint damage progression by number of risk factors (Ratingen score).

The probability for joint damage progression increased with an increasing level of DAS and also with an increasing number of risk factors. This is depicted in the margins of figure 2. Thus, at the same DAS level patients had a higher probability for joint damage progression when more baseline risk factors were present (Figure 2). Low DAS or lower during 80% of the time in the first 3 years of disease corresponded with a probability of 0.0 in patients with 0 risk factors, a probability of 0.08 in patients with 1 risk factor, 0.20 when 2 risk factors were present and 0.58 in case 3 risk factors were present. Similarly, a higher probability was seen with an increasing number of risk factors in moderate and high DAS-categories.

The predicted probabilities for joint damage progression for each risk profile and DAS category were translated into personalized treatment targets. A cut point of the risk for joint damage progression was arbitrarily set at 0.20, which was considered acceptable for now. For patients with 0 risk factors this meant that moderate DAS should be strict enough as a treatment target. Patients with 1 or 2 risk factors should reach low disease activity and for patients with 3 risk factors low DAS is not even strict enough and stricter targets should be achieved. In figure 3 the relation between DAS-level over time and the risk for joint damage progression is shown for the 4 risk groups. This shows that the differentiation of treatment targets for patients with a different number of baseline risk factors was also true for cut points higher or lower than 0.20. Sensitivity analyses with the median and maximum DAS, instead of the 80th percentile, showed a similar gradient of probabilities, but resulted in different treatment targets.

Risk factors Medication	Total (260)	0 (n=31)	1 (n=79)	2 (n=86)	3 (n=64)
% DMARD combi	17%(44)	13%(4)	14%(11)	17%(15)	22%(14)
% DMARD mono	79%(205)	74%(23)	79%(62)	81%(70)	78%(50)
% mtx	40%(104)	45%(14)	29%(23)	45%(39)	44%(28)
% prednisone < 15mg/dy	11%(28)	0%(0)	6%(5)	12%(10)	20%(13)
% prednisone ≥ 15 mg/dy	8%(21)	7%(2)	14%(11)	8%(7)	2%(1)

Table 2. Medication use of the study population, by number of risk factors. Use of synthetic DMARDs and maximum dose of prednisone in the study population between 0 and 36 months, in percentage (number of patients).

Number of risk factors (260)	Low DAS (80)	Mod DAS (102)	High DAS (78)	**Mean risk**	
0 (31)	0.00 (11)	0.06 (16)	0.50 (4)	**0.09**	
1 (79)	0.08 (37)	0.35 (23)	0.47 (19)	**0.25**	
2 (86)	0.20 (20)	0.63 (41)	0.80 (25)	**0.58**	
3 (64)	0.58 (12)	0.77 (22)	0.90 (30)	**0.80**	
Mean risk	**0.17**	**0.51**	**0.74**		

Figure 2. Probability for joint damage progression by number of risk factors and DAS level. Probability for joint damage progression for different number of risk factors and different levels of DAS between 6 and 36 months. The number of risk factors regards anti-CCP positivity, ESR > 25 mm/h and ≥ 1 erosion at baseline. Low DAS < 2.4, moderate DAS 2.4-3.7, high DAS > 3.7.

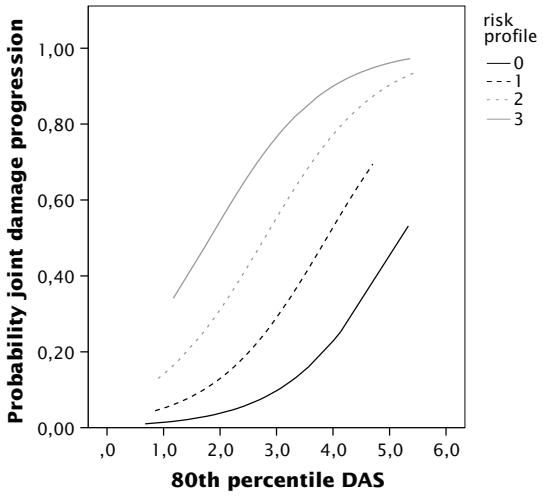

Figure 3. Probability curve for joint damage progression for four risk groups with 0, 1, 2 or 3 risk factors at baseline.

Discussion

Complete absence of symptoms, preferably without medication, is the ultimate goal in the treatment of RA. The treatment target in the starting phase of RA is therefore DAS remission. However, usually sustained remission is hard to achieve with the treatment options currently available.[8] According to the results of this study, remission is not needed in all RA patients from the viewpoint of prevention of joint damage progression.

An increasing level of DAS over time and an increasing number of risk factors at baseline were associated with a higher probability for joint damage progression after 3 years. Patients with more risk factors had a higher probability for joint damage progression at the same DAS-level over time. In a subgroup of patients with 0 risk factors for joint damage progression the treatment target can be adapted to moderate disease activity, while the chance of developing joint damage progression is quite low. For patients with 1 or 2 risk factors a more stringent target should be aimed for and low DAS should be achieved as soon as possible. In patients with three risk factors, low disease activity is not strict enough to prevent joint damage progression in the majority of these patients.

The clinical implication of this study is that not all patients need to achieve clinical remission to avoid joint damage progression. In a personalized treatment target the prognostic profile of the individual patient is taken into account. The treatment target and the need for therapy change should be subject of discussion between rheumatologist and patient. This might

bridge the gap between the patient acceptable symptom state (PASS), which is often at the level of moderate DAS, and the guidelines that advise DAS remission, also in patients with a low risk for unfavourable prognosis.[11] In other cases, individual estimation of the prognosis might convince the rheumatologist of the importance to firmly suppress disease activity, because underappreciation of the risk and outdated treatment still lead to poor outcomes.[4]

The importance to measure and use anti-CCP, ESR and erosions at baseline was confirmed in this study, not only for the prognosis at baseline, but also when setting an individual treatment target. The same was true for the association between DAS and joint damage progression. Two important steps were made in this study to support application of this knowledge in clinical practice: 1) the use of a simplified baseline prediction model and 2) the translation to personalized treatment targets based on the probability for joint damage progression. Personalized medicine in RA focuses on optimal pharmacotherapy algorithms and predictors for response and side effects.[30] In this study we showed that the personalized approach can also be used when setting a personalized treatment target.

In current daily practice rheumatologists often accept low or moderate disease activity in an individual patient with few symptoms, especially when X-ray or Ultrasound show neither erosions, nor power Doppler activity. The results of this study confirm this practical way of dealing with the current guidelines. Moreover, this approach opens up the possibility to quantify the risks of joint damage progression, extending beyond the experience of individual rheumatologists.

The aim of the study was to show a practical way of personalized medicine. Several steps need to be taken before definitive treatment targets for clinical practice can be defined. The simplified baseline prediction model needs to be externally validated and the equal importance that was given to anti-CCP, ESR and erosions at baseline should be checked in another population. Because treatment influences the relation between disease activity and joint damage progression, treatment targets might differ between patients on DMARD therapy and patients on biologic therapy. This should be considered in a validation study by stratification of the treatment given. In the future other promising prognostic factors may be added for refinement of the model, like ultrasound of an index joint.[31] Also the category DAS < 2.4 could be divided into remission and low disease activity. Because of the small study population this was not possible in this study. Studies about the importance of inflammation of the feet joints for the prediction of joint damage progression and defining remission have contradicting results. We therefore chose to use the full DAS in this prediction model and not the more frequently used DAS28.[32,33] Application of this principle to DAS28 and other indices of disease activity used for treat-to-target is a logical next step.

Progression of joint damage was the only outcome measure considered in this study, since this is currently the focus of treatment. However, other consequences of RA like functional disability and extra-articular features like lymphomas or atherosclerosis are important when defining treatment targets. The treatment target for prevention of cardiovascular diseases may differ from the target for prevention of joint damage. This should be taken into account when defining clinical treatment targets. Also patient's comfort and fatique should be considered.

In this study the Ratingen score was used for evaluation of X-rays and not the modified Sharp score. This could be seen as a limitation of this study. The main differences between these two scores are that in the Ratingen score the percentage of eroded joint surface is evaluated instead of the number of erosions and that joint space narrowing (JSN) is not evaluated in the Ratingen score. However, Ratingen score and modified Sharp are closely correlated because the same joints are evaluated and because of the relative weight that is given to erosions versus JSN in the Sharp van der Heijde score.[34-37]

Ideally, prognostic models are developed in patients who are untreated, ie. follow the natural course of disease. The advantage of an older cohort that is less intensively treated is that it resembles the natural course of RA as close as possible and is more sensitive for differences between the risk groups. The risk for and amount of joint damage progression in more recently diagnosed RA patients is expected to be lower due to earlier diagnosis, better treatment and possibly a milder disease course.[38,39] Therefore, the generalizability of the results to more recent cohorts is limited. It is however expected that the gradient of probability with more risk factors and at higher levels of disease activity will still be there. A limitation of the older cohort and the observational study design is that treatment was not randomized in the four risk groups. Patients treated with biologics were excluded in our analyses. These patients probably had a worse prognosis. Because it concerns only 9 patients this exclusion criterion has not influenced the results of the analyses.

The 80th percentile of the DAS was used in the analyses, representing the DAS over time between 6 and 36 months. The purpose of a target is that most observations should be below target. The maximum DAS could overestimate the level of disease activity in an individual patient. The median DAS does not reflect a treatment target because half of the observations are above the median. Sensitivity analyses with the median and maximum DAS showed a similar gradient of probabilities for joint damage progression, when more baseline risk factors were present and at higher levels of DAS, but resulted in different treatment targets because of other probabilities.

In conclusion, in RA personalized treatment targets can be defined, based on the combination of baseline risk factors and disease activity over time. Presence of persisting disease activity with one or more risk factors is an indication to treat to a more intensive target. In further research the concept and treatment targets should be validated and other outcomes, such as cardiovascular risk and function, should be studied. This should be the base for a personalized treat-to-target approach in RA.

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Susie: Mw Bearing, is het uw infuus dat piept om 4 uur 's morgens?

(ze checkt het slangetje, het alarm stopt) Heb ik u wakker gemaakt?

Vivian: Ik was al wakker

Susie: Wat is er aan de hand, lieverd?

Vivian: *(tegen publiek)* denk niet dat ik me ooit door iemand lieverd laat noemen, maar ik vond het op dat moment geen probleem.*(tegen Susie)* Ik weet het niet.

Susie: Kan je niet slapen?

Vivian: Nee, ik blijf maar piekeren

Susie: En als je veel piekert, raak je in de war

Vivian: Ik weet het. Ik kom er niet uit.

Susie: waar je doorheen gaat is moeilijk

Vivian: Ik ben dol op moeilijke dingen

Susie: Maar dat is niet hetzelfde. Het is alsof je de controle kwijt bent, of niet?

Vivian: Ik ben bang

Susie: O lieverd, natuurlijk ben je bang

Vivian: Ik wil…

Susie: Ik weet het, het is moeilijk

Vivian: Ik ben niet meer zeker van mezelf

Susie: En dat ben je wel gewend

Vivian: Ja, ik was altijd zeker van mezelf

Fragment uit *Als de dood*, Albert Verlinden Entertainment 2010

General discussion

6

The ultimate goal in Rheumatoid Arthritis (RA) is to achieve complete, drug free remission. Despite the many available treatment options, drug free remission yet is rarely achieved in clinical practice. Therefore a surrogate treatment target is used: clinical remission, meaning the virtual absence of clinical signs and symptoms of disease. Several criteria systems have been devised to define clinical remission and also low disease activity as clinical remission is also hard to achieve. Notably, even in the most strict remission criteria, residual disease activity is allowed for.[1] The concept of remission or low disease activity is important as it depicts a target for treatment. In RA, patients are effectively treated according to the principle of treat-to-target.[2-5] Currently, in the guidelines for the management of RA this treatment target is regarded to be the same for all patients: 'one size fits all'.[6-8] The aim of this thesis was to show how disease activity targets for the treat-to-target strategy in RA can be personalized. The way we tried to realize this was by quantifying the individual risk for joint damage progression in RA during the first three years of the disease. This individual risk was based on the three main prognostic factors for joint damage progression: anti-cyclic citrullinated peptide (anti-CCP), acute phase reactant and erosiveness at the time of diagnosis. Next, it was studied how the individual risk for an unfavorable prognosis could be translated into an individual disease activity treatment target for the prevention of joint damage progression.

In this thesis some important steps have been made for personalization of the target in the current treat-to-target strategies. 1) It was shown that anti-CCP negative RA patients have a higher 'tolerable' level of disease activity regarding joint damage than anti-CCP positive patients. 2) It was shown that when two or three of the risk factors are present in a patient, the prognosis is worse than when only one of the main risk factors is present. 3) It was shown that prediction models for joint damage, based on the three main risk factors, could be simplified without loss of performance. 4) It was shown how a suitable and personal treatment target could be set, based on the individual risk profile at baseline.

Several risk matrices for use in clinical practice were previously developed, with the aim to further differentiate the dichotomy of being at risk versus not being at risk for joint damage progression and to quantify this risk.[9-12] The baseline model developed in this thesis is more simple than the previously developed matrices, with the double aim to be easy to use in practice and to be better generalizable by being less prone to overfitting. Apparently, simplification occurred at no loss of performance. Most importantly, through simplification the treatment target for an individual patient is adjusted according to the baseline risk factors as shown in this thesis.

What this thesis adds
• Anti-CCP negative RA patients have a higher 'tolerable' level of disease activity than anti-CCP positive patients, regarding joint damage progression. • When two or three of the main risk factors for joint damage progression are present in an RA patient, the prognosis is worse than when only one of the risk factors is present. • A prediction model based on three main risk factors for joint damage progression in RA, can be simplified without loss of performance. • In RA, a suitable and a personal treatment target can be set, based on the individual risk profile.

RA is a heterogenous disease in clinical presentation and in prognosis. The development of Rheumatoid Factor (RF) and anti CCP tests as well as the ACR and recent EULAR/ACR criteria have made it possible to further differentiate two subtypes of RA.[13-15] In this thesis we elaborated on this by further categorizing patients regarding the prognosis for joint damage progression. The differentiation in this thesis, based on quantification of the risk for joint damage progression, is important for the choice of an appropriate treatment target in clinical practice. In addition, it facilitates the communication between the rheumatologist and the patient regarding the individual prognosis. In evidence-based medicine, results attained in a group of patients are generalized to individual patients. When the individual patient is similar to that group of patients regarding baseline risk factors and the level of inflammation, the chances for good or unfavorable prognosis of the individual will also resemble the prognosis of that group. Therefore, differentiation of the type of RA is important for more personalized and evidence based treatment strategies.

One of the main principles of the EULAR guidelines for the management of RA is that patients should participate in decision-making.[7] This is facilitated when the risks and benefits of different options of treatment are clear. It will be easier for the rheumatologist to convince the patient at high risk for joint damage progression that intensification of treatment is sometimes needed, despite the fact that a state of low or moderate disease activity might be acceptable from the patients point of view. In other cases, if the patient has a low chance of damage of the joints, it might help the rheumatologist to accept a certain level of inflammation if this is acceptable for the individual patient.[16,17] Good estimation of the individual prognosis of a patient can also guide the choice of therapy. In a patient with low or moderate disease activity who is not at risk for joint damage progression, intensification of DMARD therapy might not be needed and analgesics could be preferentially offered. Of course this is only true when no other consequences of disease activity are expected outside the joints, for instance a higher risk for cardiovascular disease or secondary lymphomas.

Personalization of treatment targets is a way to look at the concept of personalized medicine. The term personalized medicine implies evidence-based medicine in which the evidence for treatment decisions is based on the patients clinical, genetic and molecular features and his environment.[18,19] In general, the focus in personalized medicine appears to be on genetic and molecular research for the prediction of the response to treatment. It is hypothesized that after complete deciphering of the human genome, future disease and response to treatment could all be read in a patient's genome.[20] This is a promising perspective, also in the management of RA. However, currently there are some important barriers for the translation of the results of this basic research into clinical practice.[18,19] The barriers deal with non-replicability of findings and associations not being strong enough to help in therapy choices for the individual patient.[21] Therefore, it is important to recognize that personalized medicine covers much more than prediction of treatment response, based on molecular or genetic profiles alone. It is also about prediction of the untreated and treated disease outcome based on clinical factors, alone or in combination with knowledge about a patient's genetic and molecular background.

Research Agenda

- External validation of the simplified prognostic baseline model for joint damage progression
- External validation of the dose dependent trend in the quantified risk estimation for joint damage progression for patients with different risk profiles, as a basis for personalized disease activity treatment targets.
- Development of a prediction model for personalized treatment targets for DAS28 and SDAI.
- Evaluation of the response to treatment in patients with different risk profiles.
- Evaluation of the differences in progression of joint damage in patients treated with different sorts of medication.
- Weighing the patients PASS in the choice of the personalized treatment target
- Addition of other prognostic baseline factors to the model, such as genetic, molecular or imaging factors.

By proposing individualized treatment targets for disease activity in RA, this thesis is a further step towards personalized medicine in RA. However, the treatment targets as described in chapter 5 are not definitive and several steps should be taken to improve and adapt the prediction model. The next step in future research should focus on validation of the results in another population. Quite notably, the generalizability of earlier developed prediction matrices appeared to be limited.[22,23] This means that while these models performed well in

the sample they were developed in, they do not give correct predictions in other patients. Generalizability of our simple baseline prediction model has to be tested by external validation. The same is true for the model for differentiation in disease activity treatment targets. In more recent RA cohorts patients have been diagnosed earlier and were treated more intensively. This probably results in a lower risk for joint damage progression and in less progression if damage is present after all. However, in general a similar dose dependent increase of the risk for joint damage progression with respect to prognostic factors and disease activity is expected.

The response to a treatment might be different for patients with a different risk profile.[24] Also the consequences regarding joint damage progression at a certain level of disease activity could be different when a patient is treated with MTX or biologics. MTX is hypothesized to reduce joint damage progression by repression of disease activity, while anti-TNF supposedly not only affects disease activity, but also affects joint damage separately. Consequently, the relationship between disease activity and joint damage is modified by anti-TNF.[25,26] This effect of different medication should also be considered when setting personalized treatment targets.

The DAS is an index of disease activity that is often used in treat-to-target studies.[2,3] However, the original DAS is not often used in daily clinical practice because it contains the Ritchie score.[27] Therefore, models similar to those developed here should be developed to set treatment targets for DAS28 and SDAI, as these indices are mostly used in practice.

In using 'treat-to-target', considering patients preference is important for adherence to therapy. When the risk for joint damage progression is estimated as low and intensification of treatment is not needed, the patient acceptable symptom state (PASS) should be considered for setting a personalized treatment target. This is particularly the case in patients without risk factors and with moderate disease activity as the personalized treatment target, consequences of acceptance of this level of disease activity should be studied. On the other hand, in patients with high risk for joint damage progression, providing insight in the individualized risk for unfavourable prognosis could increase the patient's compliance.

In future versions of the RA treatment target model, other prediction factors than anti-CCP, erosiveness and acute phase reactant could be used. Ultrasound of an index joint is a possible predictor that could be added.[28] Also genetic or molecular factors or serum levels of medication could improve the predictive ability of the model.[29] The use of imaging or biomarkers is especially important in RA patients with an unfavorable prognosis, where subclinical disease activity may still lead to joint damage progression. In most of the studies in this thesis, joint damage progression is the only outcome measure taken into account, since this is the hallmark sequel in RA that is to be prevented. However, other consequences

of inflammation appeared to be important in RA more recently, for example within the risk for cardiovascular disease.[30] This outcome should also be taken into account in future versions of an RA treatment target model.

In conclusion, next to response to treatment and toxicity of treatment, the two main branches of research in personalized medicine in RA, a third branch of research should be further developed: personalization of the treatment target. The current focus in personalized medicine is on genetic and molecular profiles. These profiles are promising for the future and should be further developed into clinical useful prognostic models. However, we should realize that an enormous amount of information is hidden in the clinical prognostic factors that are generally known in RA. Finding ways to combine these clinical prognostic factors will bring personalized medicine in RA sooner to daily clinical practice.

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Ik daar op het bankje in het park vrij en alleen lijkt elke meter een kilometer geworden elke stap een ruimtereis

Wat niemand aan mij ziet als ik op zo`n bankje zit in het park is dat ik een lange afstandsrenner ben

Dromen over de toekomst is soms nog moeilijk ik kom van heel ver maar ik ben er wel

Fragment uit *Wie is er nou gek of is ik een ander*.
rotterdamscentrumvoortheater 2014.

Summary

7

Rheumatoid Arthritis (RA) is a systemic disease that is characterized by symmetric joint inflammation. The inflammation can lead to joint damage involving cortical bone and cartilage. To prevent joint damage, the ultimate goal in the treatment of RA is to achieve complete, drug free remission. Despite the many available treatment options, in practice this still appears to be nearly impossible. Therefore a surrogate treatment target is used: clinical remission, meaning virtual absence of clinical signs and symptoms. Clinical remission is defined by several criteria that differ in the level of residual disease activity that is considered acceptable. The criteria that are more easily fulfilled in the management of RA are associated with the presence of (more) residual disease activity. In contrast, stricter criteria show limited residual disease activity, but are hardly reached in clinical practice. A treatment target that is suitable for one patient might be too strict or not strict enough for another patient. The question 'what is a suitable treatment target for whom?' should therefore be the subject for discussion about personalized medicine in RA. The aim of this thesis was therefore to show how disease activity treatment targets in RA could be personalized.

Anti-CCP is an important prognostic marker for joint damage progression in RA. When comparing anti-CCP positive and anti-CCP negative RA patients, anti-CCP negative patients have a lower progression rate for joint damage, compared to anti-CCP positive patients, at the same level of inflammation. From the point of view of prevention of joint damage, this would mean that the acceptable level of disease activity in anti-CCP negative patients is higher than in anti-CCP positive patients, resulting in the same risk for joint damage progression. Less stringent treatment targets could therefore be used in anti-CCP negative patients and low disease activity might be an alternative treatment target for remission.

Next to anti-CCP, presence of erosions and high levels of acute phase reactant at baseline are the main prognostic factors for joint damage progression. When setting personalized treatment targets, these two factors should also be taken into account. Several prognostic models have been previously developed with anti-CCP, erosions and acute phase reactant in early RA cohorts. However, these models had limited validity when applied in external samples. This means that the models do not give sufficiently correct predictions in other patients than the population that they were developed in. In general, generalizability is better in a simple model because simplification corrects for overfitting. An extended prediction model was developed, in which the level of the three risk factors was compared to a simplified model, in which only the number of risk factors was counted. Simplification of the baseline prediction model appeared to be possible without loss of discriminative ability and thus the predictive value, as compared to a more detailed prediction model.

The three risk factors can also be used for setting personalized treatment targets in RA. Based on the simplified baseline prediction model for joint damage progression, four risk groups were defined, based on the number of risk factors (0 to 3) a patient had at baseline. The risk for joint damage progression incrementally increased when more risk factors were present. A higher risk for joint damage was also seen at a higher level of disease activity over time, also in a dose dependent way. The combination of the baseline risk and the level of disease activity over time resulted in quantification of the probability for joint damage progression. A patient with more than one risk factor had a higher risk for joint damage progression at a certain level of disease activity, compared to a patient without or with only one baseline risk factor at the same level of disease activity. The treatment target for disease activity should therefore be lower in patients with more risk factors, with the aim of preventing joint damage progression. This concept should be the basis for personalized treatment targets in RA.

In this thesis the first steps have been taken towards personalized treatment targets. The focus in personalized medicine is currently on genetic and molecular markers. Personalizing treatment targets based on clinical factors is a new way to look at the concept of personalized medicine in RA. Although several steps still need to be taken for improvement and refinement of the presented models, personalized medicine for RA may be closer than we think.

Mijn vader zegt
dat ik het als een wedstrijd moet zien
Ik moet dus helemaal niks
Moeten is zo ouderwets
Er zijn ***kansen en risico's*** zegt hij
die risico's moet je onder ogen zien
in kaart brengen en bevechten
Face your enemy
Dat vind ik dus niet
je moet relaxed zijn
anders ontgaan je de leukste dingen

Fragment uit *Candy*, Izaira Kersten en Floris van Tilburg 2010

Samenvatting

8

Op de voorkant van dit proefschrift staat het schilderij *Winterlandschap met schaatsers* afgebeeld, van Hendrick Avercamp (ca 1608), een meesterwerk uit de 17e eeuw dat in de eregalerij van het Rijksmuseum wordt tentoon gesteld. Wat dit schilderij bijzonder maakt, is dat je er op verschillende manieren naar kunt kijken. Bij de eerste blik zie je een winterlandschap met schaatsers. Maar als je beter kijkt, zie je verschillen tussen de mensen op het ijs. En hoe langer je kijkt, hoe meer je ziet.

Ook naar patienten met Reumatoide Artritis (RA) kan je op verschillende manieren kijken. Wat voor alle RA patienten geldt, is dat het gaat om een chronische ziekte, die ontstaat doordat het afweersysteem zich richt tegen het eigen lichaam. Hierdoor ontstaat ontsteking van de gewrichten, die leidt tot pijn en stijfheid. Op langere termijn kan dit leiden tot beschadiging van bot en kraakbeen, waardoor de gewrichten minder goed functioneren. RA kan niet worden genezen. De behandeling richt zich daarom op het onderdrukken van de ontsteking en het verlichten van de pijnklachten. Het niveau waarop de patiënt (bijna) geen merkbare ontsteking meer heeft en de kans op lange termijn schade verwaarloosbaar is wordt 'klinische remissie' genoemd. Dit is het ultieme behandeldoel voor alle RA patienten. Er zijn echter ook grote verschillen tussen RA patienten. Deze verschillen gaan over de mate en fluctuatie van de gewrichtsonsteking en de prognose wat betreft de lange termijn gevolgen zoals gewrichtsschade.

Waar het schilderij *Winterlandschap met schaatsers* pas echt tot leven komt bij het bestuderen van de afzonderlijke schaatsers, is het bij RA belangrijk om naar de individuele patiënten te kijken en rekening te houden met de variatie in de prognose en het ziektebeloop. Klinische remissie is voor een minderheid van de RA patienten een haalbaar behandeldoel. De vraag die centraal staat in dit proefschrift is daarom of er gedifferentieerd kan worden in het behandeldoel van RA.

Er zijn verschillende behandelingen mogelijk bij RA. Hoe een patiënt op een bepaald medicijn reageert, is niet goed te voorspellen. Een bepaald medicijn kan bij de ene patiënt de ontsteking goed onderdrukken zonder dat er sprake is van bijwerkingen, terwijl hetzelfde medicijn bij een andere patiënt niet effectief is en veel bijwerkingen geeft. Daarom wordt veel onderzoek gedaan om de medicatie bij RA beter af te stemmen op de individuele patiënt. Dit wordt personalized medicine genoemd, een persoonsgerichte benadering bij het bepalen van de beste behandeling. De nadruk bij personalized medicine ligt op het zoeken naar welke genen in het DNA kunnen voorspellen welk medicijn de grootste kans geeft op klinische remissie en de kleinste kans op bijwerkingen bij de individuele patiënt. Dit is een veelbelovende tak van onderzoek. Maar helaas is deze kennis op dit moment nog niet toepasbaar omdat het ver af staat van de klinische praktijk.

Personalized medicine is echter meer dan het voorspellen van het effect van medicatie op basis van een genetisch profiel. Beslissingen over de beste behandeling voor een individuele patient kunnen ook worden genomen op basis van klinische, moleculaire en omgevingsfactoren en op wat bekend is over de onbehandelde prognose van de patient. Zo zijn er verschillende risicofactoren aan het begin van de ziekte die in verband worden gebracht met een grote kans op het ontwikkelen van gewrichtsschade op lange termijn. Dit zijn een hoge bloedbezinking, aanwezigheid van erosies (gewrichtsschade van het bot) en aanwezigheid van anti-CCP. Anti-CCP zijn antistoffen tegen CCP, een eiwit dat alleen voorkomt bij mensen met RA. Deze drie risicofactoren zijn in de huidige behandelrichtlijnen verwerkt door een patient als 'hoog risico patient' te beschouwen als een patient *één* van deze drie risicofactoren heeft. Bij deze patienten wordt sneller overgegaan tot behandeling met intensievere en duurdere medicatie (biologicals) als klinische remissie niet of niet snel genoeg wordt bereikt.

Het zou mogelijk moeten zijn om personalized medicine dichter bij de praktijk te brengen met behulp van de bekende risicofactoren. In de wetenschappelijke literatuur zijn meerdere modellen beschreven waarmee de tweedeling tussen hoog en laag risico patienten uit de richtlijn verder is gedifferentieerd, door de kans op gewrichtsschade te kwantificeren. Bij het kiezen van de meest geschikte behandeling voor een individuele patient en het afwegen van de voordelen en de mogelijke nadelen van een behandeling maakt het namelijk uit of een patient 20% of 80% kans heeft op het ontwikkelen van gewrichtsschade op lange termijn.

De generaliseerbaarheid van deze modellen blijkt beperkt te zijn. Bovendien wordt alleen naar risicofactoren aan het begin van de ziekte gekeken, terwijl een heel belangrijke voorspellende factor voor gewrichtsschade de mate van ontsteking is tijdens het ziektebeloop. Dit is niet meegenomen in de modellen bij het bepalen van het risico op gewrichtsschade. De combinatie van de risicofactoren voor een slechte prognose bij het begin van de ziekte en de mate van ontsteking tijdens de ziekte bevat zinvolle informatie voor de prognose van de individuele patient. Dit zou kunnen worden gebruikt om het behandeldoel wat betreft het acceptabele ontstekingsniveau af te stemmen op de prognose van de individuele patiënt.

Voor het meten van ontsteking bestaan meerdere methoden. In dit proefschrift is uitgegaan van de Disease Activity Score (DAS). DAS en de verkorte variant DAS28 zijn internationaal veel gebruikte methodes voor het meten van ontsteking. De DAS is een cijfer tussen 0 en 10 dat wordt berekend op basis van vier componenten die de ontsteking in en buiten de gewrichten weergeven: 1) het aantal gezwollen gewrichten, 2) het aantal pijnlijke gewrichten, 3) de bloedbezinking 4) de beoordeling van de patiënt hoe hij of zij

zich voelt. In de praktijk werken reumatologen met twee waarden: DAS kleiner dan 1.6, wat 'klinische remissie' wordt genoemd, en DAS tussen 1,6 en 2,4, wat 'lage ziekteactiviteit' heet. Deze getallen zijn belangrijk voor de arts, omdat op basis hiervan wordt besloten of de behandeling moet worden aangepast en een hogere dosering of sterker medicijn moet worden voorgeschreven.

Bij de diagnose RA wordt onderscheid gemaakt in twee typen: anti-CCP positieve en anti-CCP negatieve RA. Anti-CCP positieve patienten, hebben vaak meer ontsteking dan anti-CCP negatieve patienten en meer ontsteking leidt tot meer gewrichtsschade. Echter, ook op hetzelfde ontstekingsniveau blijkt bij anti-CCP positieve patienten meer gewrichtsschade te ontstaan dan bij anti-CCP negatieve patienten. Dit is daarom een belangrijke voorspellende factor voor het ontstaan of verergeren van gewrichtsschade. Het ontstekingsniveau waarop schade ontstaat bij anti-CCP positieve patiënten ligt dus lager dan bij anti-CCP negatieve patiënten. Het niveau van ontsteking dat als acceptabel beschouwd kan worden ligt daarom ook lager bij anti-CCP positieve patiënten dan bij de anti-CCP negatieve patiënten.

Naast anti-CCP zijn de aanwezigheid van erosies en een hoge bloedbezinking op het moment van diagnose de belangrijkste voorspellende factoren voor het ontstaan of verergeren van gewrichtsschade op lange termijn. De modellen waarin deze voorspellende factoren zijn verwerkt bleken echter onvoldoende generaliseerbaar te zijn. Vereenvoudiging van een model draagt bij aan een betere generalizeerbaarheid. De bestaande voorspelmodellen met anti-CCP, erosies en bezinking als voorspellende factoren zijn daarom in dit proefschrift vereenvoudigd. Een model waarin alleen de aanwezigheid van de drie voorspellende factoren werd geteld en vertaald in een risicoscore van 0, 1, 2 of 3, bleek evengoed de prognose te kunnen voorspellen als een uitgebreid model waarin de hoogte van de drie genoemde risicofactoren in meer detail werd meegewogen. Deze vereenvoudiging zou kunnen bijdragen aan betere generaliseerbaarheid van de voorspellingen van het model en daarnaast zorgen voor een verdere differentiatie van het huidige onderscheid tussen hoog- en laagrisicopatiënten naar een classificatie met vier risiconiveaus bij het stellen van de diagnose RA.

Deze differentiatie met de vier risicogroepen aan het begin van de ziekte kan vervolgens gebruikt worden voor het bepalen van een persoonlijk behandeldoel in RA. De kans op gewrichtsschade is groter als patiënten in een hogere risicogroep zitten, dus meer risicofactoren hebben aan het begin van het ziekteproces. De kans op gewrichtsschade wordt ook hoger bij een hogere DAS, dus bij meer ontsteking. Door dit te combineren kan de kans op schade bij verschillende ontstekingsniveaus berekend worden. Ter illustratie, een patiënt met 0 risicofactoren heeft volgens dit model 0% kans op gewrichtsschade bij een lage DAS, een patiënt met 1 risicofactor heeft een kans van 8% op schade bij een lage DAS, een patiënt met 2 risicofactoren heeft op dit ontstekingsniveau 20% kans op schade, terwijl dit voor een

patiënt met 3 risicofactoren al boven de 50% ligt. Afhankelijk van hoeveel risico door de arts en patiënt geaccepteerd wordt, zou het behandeldoel wat betreft de mate van restontsteking die acceptabel is om gewrichtsschade te voorkomen, strenger moeten zijn voor patiënten met meer risicofactoren, bijvoorbeeld DAS < 1.6 voor patiënten met 3 risicofactoren, DAS < 2.4 zou streng genoeg kunnen zijn voor patiënten met 1 of 2 risicofactoren, en bij een patiënt met 0 risicofactoren zou een DAS iets boven 2.4 zelfs acceptabel kunnen zijn. Veel patiënten voelen zich al prettig bij een DAS-nieau iets hoger dan 2.4. Als een patient een hoog risico heeft op gewrichtsschade geeft dit model de reumatoloog argumenten om te patient te overtuigen waarom het toch belangrijk is om het ontstekingsniveau verder te onderdrukken. Bij patienten met een laag risico, kan op basis van dit model juist meer ontsteking geaccepteerd worden, als de patient zich hier goed bij voelt.

Wat het schilderij van Avercamp laat zien, is dat je door goed te kijken kunt differentiëren tussen individuen. Dit proefschrift beschrijft hoe ook in een groep RA patienten gedifferentieerd kan worden door goed kijken naar wat we al weten over de verschillende risicofactoren voor gewrichtsschade op lange termijn en deze kennis op een juiste wijze te combineren. Dit kan helpen bij het bepalen van een geschikt behandeldoel voor de individuele patient in het gesprek tussen arts en patiënt en bij het beslissen of aanpassing van de medicatie nodig is. De focus in 'personalized medicine' ligt momenteel bij het zoeken naar genetische en moleculaire factoren die de respons en toxiciteit van medicatie kunnen voorspellen. Dit staat echter nog ver van de klinische praktijk. Door beter te kijken naar wat we wel al weten over de prognostische factoren, is personalized medicine wellicht dichter bij dan tot nu toe werd gedacht. Het individualiseren van behandeldoelen gebaseerd op anti-CCP, erosies en bezinking is een veelbelovende manier om te kijken naar het concept personalized medicine bij RA, omdat dit eenvoudig valt te integreren in de praktijk en daarnaast goedkoper is dan genetisch onderzoek. Hoewel er nog een aantal stappen gezet moeten worden voor verbetering en verfijning van de gepresenteerde modellen voor deze in de klinische praktijk gebruikt kunnen worden, zou dit concept de basis kunnen zijn voor het bepalen van individuele behandeldoelen in RA.

Een uit de kluiten gewassen viool
hij kwam met de wind mee
om de muziek goed hoorbaar te maken
de muziek is voor ons allemaal
mooie klassieke melodieën
op de woelige baren achter de rots
we spelen wat in me op komt
we horen trommelen
er komt water over ons heen
tot je niets meer hoort
spelend op de zeebodem
hoe zal dat klinken?
borrelen

Fragment uit serie *Timeslips*. HoutenBeenTheater 2014

Epiloog

‘Wil je cliniclown worden?’ was een veelgehoorde reactie wanneer ik vertelde dat ik naast het promotieonderzoek bij de afdeling Reumatische Ziekten, twee dagen in de week theaterwetenschap studeerde. Dit geeft aan dat geneeskunde en theater twee vakgebieden zijn die voor veel mensen, ook voor artsen, ver uit elkaar liggen. Door het parallel lopen van het promotieonderzoek en de studie theaterwetenschap, heb ik het raakvlak tussen deze vakgebieden nader kunnen verkennen. Niet geheel toevallig ben ik tot de conclusie gekomen dat één van de punten waar geneeskunde en theater elkaar raken, ligt op het vlak van personalized medicine.

In dit proefschrift wordt het begrip personalized medicine in een bredere context geplaatst en wordt beschreven dat personalized medicine niet alleen gaat om de behandeling zelf, maar ook om het individualiseren van het doel van de behandeling. De nadruk ligt hier nog steeds op de medische kant. Dat wat voor de dokter vanuit medisch oogpunt belangrijk is, is echter niet altijd belangrijk voor de persoon die behandeld wordt. Meestal gaat het hierbij om niet-medische dingen. Om als arts een patiënt goed te kunnen helpen, is het belangrijk om je dit te realiseren. Zo kan het voor de ene patiënt belangrijk zijn om muziek te kunnen blijven maken, omdat dit zijn werk of hobby is, en is een andere patiënt bang om de controle te verliezen. Als je als arts weet wat voor de patiënt belangrijk is, kan je hier beter op inspelen en over communiceren met de patiënt.

Theater is een krachtig communicatiemiddel, een spiegel van de maatschappij. Theatervoorstellingen die gaan over de gezondheidszorg zijn vaak een spiegel van de dokterspraktijk. Tijdens mijn promotietraject heb ik meerdere theatervoorstellingen en theaterprojecten gezien over de gezondheidszorg, waarbij de patiënt centraal wordt gesteld. Doordat het perspectief in deze voorstellingen bij de patiënt wordt gelegd, krijg je als publiek de kans om de situatie vanuit de positie van de patiënt te bekijken. Zo krijg je inzicht in wat voor deze persoon belangrijk is, wat hem drijft of waar zijn angsten liggen. Passages uit enkele van deze voorstellingen en projecten zijn ter illustratie in dit proefschrift opgenomen. Deze voorstellingen hebben mij geïnspireerd tijdens het onderzoek en geholpen om het uiteindelijke doel te blijven zien: de optimale behandeling voor de patiënt op elk gebied.

Dankwoord

De dag waarop ik deze promotie begon, dacht ik dat promoveren een leertraject was op het gebied van methodologie, epidemiologie en schrijfvaardigheden. Zes jaar later weet ik dat promoveren ook gaat over projectmanagement, plannen, presenteren en het verkopen van je onderzoek. Ik heb geleerd dat kunst en wetenschap meer raakvlakken hebben dan vaak wordt gedacht en ik weet nu dat de woorden “bijna klaar” voor meerdere interpretaties vatbaar zijn. Direct en indirect hebben veel mensen een bijdrage geleverd aan dit proefschrift. Ik wil iedereen daarvoor hartelijk bedanken en enkele mensen in het bijzonder.

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Bij de overstap van het Radboud UMC naar de Dienst Gezondheid en Jeugd ZHZ en later de GGD Rotterdam Rijnmond was dit proefschrift nog niet helemaal afgerond. Marieke, Arjan, Ingrid, Lenneke, Carola, Marjon, Cisca en Karin, bedankt voor de tijd die ik heb gekregen voor de afronding van dit proefschrift en de interesse waarmee jullie de laatste fase van dit project gevolgd hebben.

Ik wilde in dit boekje graag een klein stukje laten zien van wat er op het gebied van thater gebeurt in de Nederlandse gezondheidszorg. Kees Deenik, Hanna Maria Trap en Walter Supèr, bedankt voor de boeiende gesprekken die ik met jullie heb gevoerd over de toepassing van theater in de gezondheidszorg. Daarnaast wil ik alle betrokkenen bedanken voor het beschikbaar stellen van de scripts van Plezant, HoutenBeenTheater, Formaat, Suikerwerken en het rotterdamscentrumvoortheater om te gebruiken in dit proefschrift.

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Curriculum Vitae

Yvonne Vendrig – de Punder, de schrijfster van dit proefschrift, werd geboren op 7 augustus 1981 in Cuijk. Ze behaalde in 1999 haar VWO-diploma aan het Merletcollege in Cuijk, waarna ze geneeskunde ging studeren aan de Radboud Universiteit in Nijmegen. Na het doctoraal examen heeft ze in 2003 een semester Frans gestudeerd in Montpellier (Frankrijk), waarna ze in 2004 startte met haar coschappen. Vanuit haar interesse op het gebied van handchirurgie volbracht ze het keuzecoschap op de afdeling Plastische Chirurgie van het Jeroen Bosch Ziekenhuis in Den Bosch en het afsluitende coschap op de afdeling Plastische Chirurgie van het Universitair Medisch Centrum Sint Radboud. In 2006 studeerde ze af, waarna ze als arts (ANIOS) ging werken ze op de afdeling Algemene Chirurgie van het Slingeland ziekenhuis in Doetinchem. In 2007 deed ze een jaar ervaring op in de handchirurugie bij SOS Main in Straatsburg (Frankrijk). In 2008 werkte ze op de afdeling Plastische Chirurgie en Handchirurgie van het Erasmus Medisch Centrum in Rotterdam.

De theoretische achtergrond van het functioneren van het bewegingsapparaat bleek meer haar interesse te hebben dan de chirurgische praktijk en in 2009 begon Yvonne's carrière in de reumatologie. Ze werkte enkele maanden als ANIOS bij het Maasstad Ziekenhuis in Rotterdam, om later dat jaar te starten met het promotieonderzoek getiteld 'Personalized treatment targets in rheumatoid arthritis' aan de Radboud Universiteit in Nijmegen. De resultaten van het promotieonderzoek zijn beschreven in dit proefschrift. Parallel aan het promotieonderzoek, van 2010 tot en met 2013, studeerde ze Theaterwetenschap aan de Universiteit van Amsterdam. Ze schreef een scriptie over de toepassing van het 'Theater van de Onderdrukten' in de Nederlandse gezondheidszorg en rondde daarmee de bachelorstudie succesvol af.

Affiniteit met communicatie en epidemiologie was de reden voor haar overstap naar de publieke gezondheidszorg. Sinds 2013 is ze werkzaam op het gebied van milieu en gezondheid, aanvankelijk bij de Dienst Gezondheid en Jeugd in Dordrecht en later bij de GGD Rotterdam Rijnmond. In 2014 startte ze met de medische vervolgopleiding Maatschappij en Gezondheid, met het profiel medische milieukunde.

Yvonne is getrouwd met Bas Vendrig. Ze wonen samen met hun twee kinderen Sam (2003) en Lotte (2013) in Rotterdam.

Theaterteksten

1 *Iedereen is een verhaal – Parkinson*. HoutenBeenTheater 2013
In samenwerking met Parkinsonnet.
Tekst en regie Kees Deenik. www.houtenbeentheater.nl

2 *Als de dood*. Albert Verlinden Entertainment 2010
Vertaling van *Wit,* geschreven door Margaret Edson 1993

3 *Dag en nacht*. Theatergroep Plezant 2009
Tekst Tom Meulman en Walter Supèr. Regie Walter Supèr. www.plezant.nl

4 *Tot er iemand langs kwam*. Theateratelier Rotterdam Zuid – Formaat 2013.
Werkplaats voor Participatief Drama.
Tekst en regie Hanna Maria Trap. www.formaat.org

5 *De limonadefabriek*. Theatergroep Plezant 2011
Co-productie met het Radboud Universitair Medisch Centrum
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7 *Wie is er nou gek of is ik een ander*. rotterdamscentrumvoortheater 2014
Tekst Shirley Gast. Regie Paul Röttger. www.rcth.nl

8 *Candy*. Izaira Kersten en Floris van Tilburg 2010
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